

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
29 November 2001 (29.11.2001)

PCT

(10) International Publication Number
WO 01/90151 A2

(51) International Patent Classification⁷: **C07K 14/00**

(21) International Application Number: PCT/US01/16766

(22) International Filing Date: 23 May 2001 (23.05.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/207,558 25 May 2000 (25.05.2000) US

(71) Applicant: SCHERING CORPORATION [US/US];
2000 Galloping Hill Road, Kenilworth, NJ 07033-0530
(US).

(72) Inventors: **HARDIMAN, Gerard, T.**; 11276 Woodrush
Lane, San Diego, CA 92128 (US). **ROCK, Fernando, L.**;
125 Cuesta Real, La Honda, CA 94020 (US). **BAZAN, J.,
Fernando**; 426 Waverley St., # 6, Palo Alto, CA 94301
(US). **KASTELEIN, Robert, A.**; 463 Summit Drive, Red-
wood City, CA 94062 (US). **HO, Stephen, W. K.**; 745
South Bernardo Ave., #A206, Sunnyvale, CA 94087 (US).
LIU, Yong-Jun; 4010 Villa Vista, Palo Alto, CA 94306
(US).

(81) Designated States (*national*): AE, AG, AI, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CZ,
DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GR, GU,
IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LU, LV,
MA, MD, MG, MK, MN, MX, MZ, NO, NZ, PL, PT, RO,
RU, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UZ, VN,
YU, ZA.

(84) Designated States (*regional*): ARIPO patent (GI, GM,
KE, LS, MW, MZ, SD, SI, SZ, TZ, UG, ZW), Eurasian
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, HU,
IT, LL, MC, NL, PL, SE, TR), OAPI patent (BF, BJ, CF,
CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:

*as to the applicant's entitlement to claim the priority of the
earlier application (Rule 4.17(iii)) for all designations*

Published:

— *without international search report and to be republished
upon receipt of that report*

*For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.*

WO 01/90151 A2

(54) Title: HUMAN RECEPTOR PROTEINS; RELATED REAGENTS AND METHODS

(57) Abstract: Nucleic acids encoding mammalian, e.g., human receptors, purified receptor proteins and fragments thereof. Anti-
bodies, both polyclonal and monoclonal, are also provided. Methods of using the compositions for both diagnostic and therapeutic
utilities are provided.

HUMAN RECEPTOR PROTEINS; RELATED REAGENTS AND METHODS

FIELD OF THE INVENTION

The present invention relates to compositions and methods for affecting mammalian physiology, including morphogenesis or immune system function. In particular, it provides nucleic acids, proteins, and antibodies which regulate development and/or the immune system. Diagnostic and therapeutic uses of these materials are also disclosed.

BACKGROUND OF THE INVENTION

Recombinant DNA technology refers generally to techniques of integrating genetic information from a donor source into vectors for subsequent processing, such as through introduction into a host, whereby the transferred genetic information is copied and/or expressed in the new environment. Commonly, the genetic information exists in the form of complementary DNA (cDNA) derived from messenger RNA (mRNA) coding for a desired protein product. The carrier is frequently a plasmid having the capacity to incorporate cDNA for later replication in a host and, in some cases, actually to control expression of the cDNA and thereby direct synthesis of the encoded product in the host.

For some time, it has been known that the mammalian immune response is based on a series of complex cellular interactions, called the "immune network". Recent research has provided new insights into the inner workings of this network. While it remains clear that much of the immune response does, in fact, revolve around the network-like interactions of lymphocytes, macrophages, granulocytes, and other cells, immunologists now generally hold the opinion that soluble proteins, known as lymphokines, cytokines, or monokines, play critical roles in controlling these cellular interactions. Thus, there is considerable interest in the isolation, characterization, and mechanisms of action of cell modulatory factors, an understanding of which will lead to significant advancements in the diagnosis and therapy of numerous medical abnormalities, e.g., immune system disorders.

Lymphokines apparently mediate cellular activities in a variety of ways. They have been shown to support the proliferation, growth, and/or differentiation of pluripotential hematopoietic stem cells into vast numbers of progenitors comprising diverse cellular lineages which make up a complex immune system. Proper and balanced interactions between the cellular components are necessary for a healthy immune response. The different cellular lineages often respond in a different manner when lymphokines are administered in conjunction with other agents.

Cell lineages especially important to the immune response include two classes of lymphocytes: B-cells, which can produce and secrete immunoglobulins (proteins with the capability of recognizing and binding to foreign matter to effect its removal), and T-cells of various subsets that secrete lymphokines and induce or suppress the B-cells and various other cells (including other T-

cells) making up the immune network. These lymphocytes interact with many other cell types.

Another important cell lineage is the mast cell (which has not been positively identified in all mammalian species), which is a granule-containing connective tissue cell located proximal to capillaries throughout the body. These cells are found in especially high concentrations in the lungs, skin, and gastrointestinal and genitourinary tracts. Mast cells play a central role in allergy-related disorders, particularly anaphylaxis as follows: when selected antigens crosslink one class of immunoglobulins bound to receptors on the mast cell surface, the mast cell degranulates and releases mediators, e.g., histamine, serotonin, heparin, and prostaglandins, which cause allergic reactions, e.g., anaphylaxis.

Research to better understand and treat various immune disorders has been hampered by the general inability to maintain cells of the immune system in vitro. Immunologists have discovered that culturing many of these cells can be accomplished through the use of T-cell and other cell supernatants, which contain various growth factors, including many of the lymphokines.

The interleukin-1 family of proteins includes the IL-1 α , the IL-1 β , the IL-1RA, and recently the IL-1 γ (also designated Interferon-Gamma Inducing Factor, IGIF). This related family of genes have been implicated in a broad range of biological functions. See Dinarello (1994) FASEB J. 8:1314-1325; Dinarello (1991) Blood 77:1627-1652; and Okamura, et al. (1995) Nature 378:88-91.

In addition, various growth and regulatory factors exist which modulate morphogenetic development. This includes, e.g., the Toll ligands, which signal through binding to receptors which share structural, and mechanistic, features characteristic of the IL-1 receptors. See, e.g., Lemaitre, et al. (1996) Cell

86:973-983; and Belvin and Anderson (1996) Ann. Rev. Cell & Devel. Biol. 12:393-416.

From the foregoing, it is evident that the discovery and development of new soluble proteins and their
5 receptors, including ones similar to lymphokines, should contribute to new therapies for a wide range of degenerative or abnormal conditions which directly or indirectly involve development, differentiation, or
10 function, e.g., of the immune system and/or hematopoietic cells. In particular, the discovery and understanding of novel receptors for lymphokine-like molecules which enhance or potentiate the beneficial activities of other lymphokines would be highly advantageous. The present
15 invention provides new receptors for ligands exhibiting similarity to interleukin-1 like compositions and related compounds, and methods for their use.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows a schematic comparison of the protein architectures of *Drosophila*, *Caenorabditis*, and human DTLRs, and their relationship to vertebrate IL-1 receptors and plant disease resistance proteins. Three *Drosophila* (Dm) DTLRs (Toll, 18w, and the Mst ORF fragment) (Morisato and Anderson (1995) Ann. Rev. Genet. 29:371-399; Chiang and Beachy (1994) Mech. Develop. 47:225-239; Mitcham, et al. (1996) J. Biol. Chem. 271:5777-5783; and Eldon, et al. (1994) Develop. 120:885-899) are arrayed beside four complete (DTLRs 1-4) and one partial (DTLR5) human (Hu) receptors. Individual LRRs in the receptor ectodomains that are flagged by PRINTS (Attwood, et al. (1997) Nucleic Acids Res. 25:212-217) are explicitly noted by boxes; 'top' and 'bottom' Cys-rich clusters that flank the C- or N-terminal ends of LRR arrays are respectively drawn by opposed half-circles. The loss of the internal Cys-rich region in DTLRs 1-5 largely accounts for their smaller ectodomains (558, 570, 690, and 652 aa, respectively) when compared to the 784 and 977 aa extensions of Toll and 18w. The incomplete chains of DmMst and HuDTLR5 (about 519 and 153 aa ectodomains, respectively) are represented by dashed lines. The intracellular signaling module common to DTLRs, IL-1-type receptors (IL-1Rs), the intracellular protein Myd88, and the tobacco disease resistance gene N product (DRgN) is indicated below the membrane. See, e.g., Hardiman, et al. (1996) Oncogene 13:2467-2475; and Rock, et al. (1998) Proc. Nat'l Acad. Sci. USA 95:588-. Additional domains include the trio of Ig-like modules in IL-1Rs (disulfide-linked loops); the DRgN protein features an NTPase domain (box) and Myd88 has a death domain (black oval).

Figures 2A-2C show conserved structural patterns in the signaling domains of Toll- and IL-1-like cytokine receptors, and two divergent modular proteins. Figures 2A-2B show a sequence alignment of the common TH domain.

DTLRs are labeled as in Figure 1; the human (Hu) or mouse (Mo) IL-1 family receptors (IL-1R1-6) are sequentially numbered as earlier proposed (Hardiman, et al. (1996) Oncogene 13:2467-2475); Myd88 and the sequences from tobacco (To) and flax, *L. usitatissimum* (Lu), represent C- and N-terminal domains, respectively, of larger, multidomain molecules. Ungapped blocks of sequence (numbered 1-10) are boxed. Triangles indicate deleterious mutations, while truncations N-terminal of the arrow eliminate bioactivity in human IL-1R1 (Heguy, et al. (1992) J. Biol. Chem. 267:2605-2609). PHD (Rost and Sander (1994) Proteins 19:55-72) and DSC (King and Sternberg (1996) Protein Sci. 5:2298-2310) secondary structure predictions of α -helix (H), β -strand (E), or coil (L) are marked. The amino acid shading scheme depicts chemically similar residues: hydrophobic, acidic, basic, Cys, aromatic, structure-breaking, and tiny. Diagnostic sequence patterns for IL-1Rs, DTLRs, and full alignment (ALL) were derived by Consensus at a stringency of 75%. Symbols for amino acid subsets are (see internet site for detail): o, alcohol; l, aliphatic; ., any amino acid; a, aromatic; c, charged; h, hydrophobic; -, negative; p, polar; +, positive; s, small; u, tiny; t, turnlike. Figure 2C shows a topology diagram of the proposed TH β/α domain fold. The parallel β -sheet (with β -strands A-E as yellow triangles) is seen at its C-terminal end; α -helices (circles labeled 1-5) link the β -strands; chain connections are to the front (visible) or back (hidden). Conserved, charged residues at the C-end of the β -sheet are noted in gray (Asp) or as a lone black (Arg) residue (see text).

Figure 3 shows evolution of a signaling domain superfamily. The multiple TH module alignment of Figures 2A-2B was used to derive a phylogenetic tree by the Neighbor-Joining method (Thompson, et al. (1994) Nucleic

Acids Res. 22:4673-4680). Proteins labeled as in the alignment; the tree was rendered with TreeView.

Figures 4A-4D depict FISH chromosomal mapping of human DTLR genes. Denatured chromosomes from synchronous
5 cultures of human lymphocytes were hybridized to biotinylated DTLR cDNA probes for localization. The assignment of the FISH mapping data (left, Figures 4A, DTLR2; 4B, DTLR3; 4C, DTLR4; 4D, DTLR5) with chromosomal bands was achieved by superimposing FISH signals with DAPI
10 banded chromosomes (center panels). Heng and Tsui (1994) Meth. Molec. Biol. 33:109-122. Analyses are summarized in the form of human chromosome ideograms (right panels).

Figures 5A-5F depict mRNA blot analyses of Human DTLRs. Human multiple tissue blots (He, heart; Br, brain;
15 Pl, placenta; Lu, lung; Li, liver; Mu, muscle; Ki, kidney; Pn, Pancreas; Sp, spleen; Th, thymus; Pr, prostate; Te, testis; Ov, ovary, SI, small intestine; Co, colon; PBL, peripheral blood lymphocytes) and cancer cell line (promyelocytic leukemia, HL60; cervical cancer, HELAS3;
20 chronic myelogenous leukemia, K562; lymphoblastic leukemia, Molt4; colorectal adenocarcinoma, SW480; melanoma, G361; Burkitt's Lymphoma Raji, Burkitt's; colorectal adenocarcinoma, SW480; lung carcinoma, A549) containing approximately 2 µg of poly(A)⁺ RNA per lane
25 were probed with radiolabeled cDNAs encoding DTLR1 (Figures 5A-5C), DTLR2 (Figure 5D), DTLR3 (Figure 5E), and DTLR4 (Figure 5F) as described. Blots were exposed to X-ray film for 2 days (Figures 5A-5C) or one week (Figure 5D-5F) at -70° C with intensifying screens. An anomalous
30 0.3 kB species appears in some lanes; hybridization experiments exclude a message encoding a DTLR cytoplasmic fragment.

SUMMARY OF THE INVENTION

The present invention is directed to nine novel related mammalian receptors, e.g., primate, human, DNAX
5 Toll receptor like molecular structures, designated DTLR2, DTLR3, DTLR4, DTLR5, DTLR7, DTLR8, DTLR9, and DTLR10, and their biological activities. It includes nucleic acids coding for the polypeptides themselves and methods for their production and use. The nucleic acids
10 of the invention are characterized, in part, by their homology to cloned complementary DNA (cDNA) sequences enclosed herein.

In certain embodiments, the invention provides a composition of matter selected from the group of: a
15 substantially pure or recombinant DTLR2 protein or peptide exhibiting identity over a length of at least about 12 amino acids to SEQ ID NO: 4; a natural sequence DTLR2 of SEQ ID NO: 4; a fusion protein comprising DTLR2 sequence; a substantially pure or recombinant DTLR3 protein or
20 peptide exhibiting identity over a length of at least about 12 amino acids to SEQ ID NO: 6; a natural sequence DTLR3 of SEQ ID NO: 6; a fusion protein comprising DTLR3 sequence; a substantially pure or recombinant DTLR4 protein or peptide exhibiting identity over a length of at
25 least about 12 amino acids to SEQ ID NO: 26; a natural sequence DTLR4 of SEQ ID NO: 26; a fusion protein comprising DTLR4 sequence; a substantially pure or recombinant DTLR5 protein or peptide exhibiting identity over a length of at least about 12 amino acids to SEQ ID
30 NO: 10; a natural sequence DTLR5 of SEQ ID NO: 10; a fusion protein comprising DTLR5 sequence; a substantially pure or recombinant DTLR6 protein or peptide exhibiting identity over a length of at least about 12 amino acids to SEQ ID NO: 12, 28, or 30; a natural sequence DTLR6 of SEQ
35 ID NO: 12, 28, or 30; a fusion protein comprising DTLR6 sequence; a substantially pure or recombinant DTLR7

protein or peptide exhibiting identity over a length of at least about 12 amino acids to SEQ ID NO: 16, 18, or 37; a natural sequence DTLR7 of SEQ ID NO: 16, 18, or 37; a fusion protein comprising DTLR7 sequence; a substantially pure or recombinant DTLR8 protein or peptide exhibiting identity over a length of at least about 12 amino acids to SEQ ID NO: 32 or 39; a natural sequence DTLR8 of SEQ ID NO: 32 or 39; a fusion protein comprising DTLR8 sequence; a substantially pure or recombinant DTLR9 protein or peptide exhibiting identity over a length of at least about 12 amino acids to SEQ ID NO: 22 or 41; a natural sequence DTLR9 of SEQ ID NO: 22 or 41; a fusion protein comprising DTLR9 sequence; a substantially pure or recombinant DTLR10 protein or peptide exhibiting identity over a length of at least about 12 amino acids to SEQ ID NO: 34, 43, or 45; a natural sequence DTLR10 of SEQ ID NO: 34, 43, or 45; and a fusion protein comprising DTLR10 sequence. Preferably, the substantially pure or isolated protein comprises a segment exhibiting sequence identity to a corresponding portion of a DTLR2, DTLR3, DTLR4, DTLR5, DTLR6, DTLR7, DTLR8, DTLR9, or DTLR10, wherein said identity is over at least about 15 amino acids; preferably about 19 amino acids; or more preferably about 25 amino acids. In specific embodiments, the composition of matter: is DTLR2, which comprises a mature sequence of Table 2; or lacks a post-translational modification; is DTLR3, which comprises a mature sequence of Table 3; or lacks a post-translational modification; is DTLR4, which: comprises a mature sequence of Table 4; or lacks a post-translational modification; is DTLR5, which: comprises the complete sequence of Table 5; or lacks a post-translational; is DTLR6, which comprises a mature sequence of Table 6; or lacks a post-translational modification; is DTLR7, which comprises a mature sequence of Table 7; or lacks a post-translational modification; is DTLR8, which: comprises a mature sequence of Table 8; or lacks a post-

translational modification; is DTLR9, which: comprises the complete sequence of Table 9; or lacks a post-translational; is DTLR10, which comprises a mature sequence of Table 10; or lacks a post-translational
5 modification; or the composition of matter may be a protein or peptide which: is from a warm blooded animal selected from a mammal, including a primate, such as a human; comprises at least one polypeptide segment of SEQ ID NO: 4, 6, 26, 10, 12, 28, 30, 16, 18, 32, 22, or 34;
10 exhibits a plurality of portions exhibiting said identity; is a natural allelic variant of DTLR2, DTLR3, DTLR4, DTLR5, DTLR6, DTLR7, DTLR8, DTLR9, or DTLR10; has a length at least about 30 amino acids; exhibits at least two non-overlapping epitopes which are specific for a primate
15 DTLR2, DTLR3, DTLR4, DTLR5, DTLR6, DTLR7, DTLR8, DTLR9, or DTLR10; exhibits sequence identity over a length of at least about 35 amino acids to a primate DTLR2, DTLR3, DTLR4, DTLR5, DTLR6, DTLR7, DTLR8, DTLR9, or DTLR10; further exhibits at least two non-overlapping epitopes
20 which are specific for a primate DTLR2, DTLR3, DTLR4, DTLR5, DTLR6, DTLR7, DTLR8, DTLR9, or DTLR10; exhibits identity over a length of at least about 20 amino acids to a rodent DTLR6; is glycosylated; has a molecular weight of at least 100 kD with natural glycosylation; is a synthetic
25 polypeptide; is attached to a solid substrate; is conjugated to another chemical moiety; is a 5-fold or less substitution from natural sequence; or is a deletion or insertion variant from a natural sequence.

Other embodiments include a composition comprising: a
30 sterile DTLR2 protein or peptide; or the DTLR2 protein or peptide and a carrier, wherein the carrier is: an aqueous compound, including water, saline, and/or buffer; and/or formulated for oral, rectal, nasal, topical, or parenteral administration; a sterile DTLR3 protein or peptide; or the
35 DTLR3 protein or peptide and a carrier, wherein the carrier is: an aqueous compound, including water, saline,

and/or buffer; and/or formulated for oral, rectal, nasal, topical, or parenteral administration; a sterile DTLR4 protein or peptide; or the DTLR4 protein or peptide and a carrier, wherein the carrier is: an aqueous compound, including water, saline, and/or buffer; and/or formulated for oral, rectal, nasal, topical, or parenteral administration; a sterile DTLR5 protein or peptide; or the DTLR5 protein or peptide and a carrier, wherein the carrier is: an aqueous compound, including water, saline, and/or buffer; and/or formulated for oral, rectal, nasal, topical, or parenteral administration; a sterile DTLR6 protein or peptide; or the DTLR6 protein or peptide and a carrier, wherein the carrier is: an aqueous compound, including water, saline, and/or buffer; and/or formulated for oral, rectal, nasal, topical, or parenteral administration; a sterile DTLR7 protein or peptide; or the DTLR7 protein or peptide and a carrier, wherein the carrier is: an aqueous compound, including water, saline, and/or buffer; and/or formulated for oral, rectal, nasal, topical, or parenteral administration; a sterile DTLR8 protein or peptide; or the DTLR8 protein or peptide and a carrier, wherein the carrier is: an aqueous compound, including water, saline, and/or buffer; and/or formulated for oral, rectal, nasal, topical, or parenteral administration; a sterile DTLR9 protein or peptide; or the DTLR9 protein or peptide and a carrier, wherein the carrier is: an aqueous compound, including water, saline, and/or buffer; and/or formulated for oral, rectal, nasal, topical, or parenteral administration; a sterile DTLR10 protein or peptide; or the DTLR10 protein or peptide and a carrier, wherein the carrier is: an aqueous compound, including water, saline, and/or buffer; and/or formulated for oral, rectal, nasal, topical, or parenteral administration.

In certain fusion protein embodiments, the invention provides a fusion protein comprising: mature protein

sequence of Table 2, 3, 4, 5, 6, 7, 8, 9, or 10; a detection or purification tag, including a FLAG, His6, or Ig sequence; or sequence of another receptor protein.

Various kit embodiments include a kit comprising a DTLR protein or polypeptide, and: a compartment comprising the protein or polypeptide; and/or instructions for use or disposal of reagents in the kit.

Binding compound embodiments include those comprising an antigen binding site from an antibody, which specifically binds to a natural DTLR2, DTLR3, DTLR4, DTLR5, DTLR6, DTLR7, DTLR8, DTLR9, or DTLR10 protein, wherein: the protein is a primate protein; the binding compound is an Fv, Fab, or Fab2 fragment; the binding compound is conjugated to another chemical moiety; or the antibody: is raised against a peptide sequence of a mature polypeptide of Table 2, 3, 4, 5, 6, 7, 8, 9, or 10; is raised against a mature DTLR2, DTLR3, DTLR4, DTLR5, DTLR6, DTLR7, DTLR8, DTLR9, or DTLR10; is raised to a purified human DTLR2, DTLR3, DTLR4, DTLR5, DTLR6, DTLR7, DTLR8, DTLR9, or DTLR10; is immunoselected; is a polyclonal antibody; binds to a denatured DTLR2, DTLR3, DTLR4, DTLR5, DTLR6, DTLR7, DTLR8, DTLR9, or DTLR10; exhibits a K_d to antigen of at least 30 μM ; is attached to a solid substrate, including a bead or plastic membrane; is in a sterile composition; or is detectably labeled, including a radioactive or fluorescent label. A binding composition kit often comprises the binding compound, and: a compartment comprising said binding compound; and/or instructions for use or disposal of reagents in the kit. Often the kit is capable of making a qualitative or quantitative analysis.

Methods are provided, e.g., of making an antibody, comprising immunizing an immune system with an immunogenic amount of a primate DTLR2, DTLR3, DTLR4, DTLR5, DTLR6, DTLR7, DTLR8, DTLR9, or DTLR10, thereby causing said antibody to be produced; or producing an antigen:antibody

complex, comprising contacting such an antibody with a mammalian DTLR2, DTLR3, DTLR4, DTLR5, DTLR6, DTLR7, DTLR8, DTLR9, or DTLR10 protein or peptide, thereby allowing said complex to form.

- 5 Other compositions include a composition comprising: a sterile binding compound, or the binding compound and a carrier, wherein the carrier is: an aqueous compound, including water, saline, and/or buffer; and/or formulated for oral, rectal, nasal, topical, or parenteral
10 administration.

- Nucleic acid embodiments include an isolated or recombinant nucleic acid encoding a DTLR2-10 protein or peptide or fusion protein, wherein: the DTLR is from a mammal; or the nucleic acid: encodes an antigenic peptide
15 sequence of Table 2, 3, 4, 5, 6, 7, 8, 9, or 10; encodes a plurality of antigenic peptide sequences of Table 2, 3, 4, 5, 6, 7, 8, 9, or 10; comprises at least 17 contiguous nucleotides from Table 2, 3, 4, 5, 6, 7, 8, 9, or 10; exhibits at least about 80% identity to a natural cDNA
20 encoding said segment; is an expression vector; further comprises an origin of replication; is from a natural source; comprises a detectable label; comprises synthetic nucleotide sequence; is less than 6 kb, preferably less than 3 kb; is from a mammal, including a primate;
25 comprises a natural full length coding sequence; is a hybridization probe for a gene encoding said DTLR; or is a PCR primer, PCR product, or mutagenesis primer. A cell, tissue, or organ comprising such a recombinant nucleic acid is also provided. Preferably, the cell is: a
30 prokaryotic cell; a eukaryotic cell; a bacterial cell; a yeast cell; an insect cell; a mammalian cell; a mouse cell; a primate cell; or a human cell. Kits are provided comprising such nucleic acids, and: a compartment comprising said nucleic acid; a compartment further
35 comprising a primate DTLR2, DTLR3, DTLR4, or DTLR5 protein or polypeptide; and/or instructions for use or disposal of

reagents in the kit. Often, the kit is capable of making a qualitative or quantitative analysis.

Other embodiments include a nucleic acid which:
hybridizes under wash conditions of 30° C and less than 2M
5 salt to SEQ ID NO: 3; hybridizes under wash conditions of
30° C and less than 2 M salt to SEQ ID NO: 5; hybridizes
under wash conditions of 30° C and less than 2M salt to
SEQ ID NO: 7; hybridizes under wash conditions of 30° C
and less than 2 M salt to SEQ ID NO: 9; hybridizes under
10 wash conditions of 30° C and less than 2 M salt to SEQ ID
NO: 11, 13, 27, or 29; hybridizes under wash conditions of
30° C and less than 2 M salt to SEQ ID NO: 15, 17, or 36;
hybridizes under wash conditions of 30° C and less than 2
M salt to SEQ ID NO: 19, 31, or 38; hybridizes under wash
15 conditions of 30° C and less than 2 M salt to SEQ ID NO:
21 or 40; hybridizes under wash conditions of 30° C and
less than 2 M salt to SEQ ID NO: 23, 33, 42, or 44;
exhibits at least about 85% identity over a stretch of at
least about 30 nucleotides to a primate DTLR2; exhibits at
20 least about 85% identity over a stretch of at least about
30 nucleotides to a primate DTLR3; exhibits at least about
85% identity over a stretch of at least about 30
nucleotides to a primate DTLR4; or exhibits at least about
85% identity over a stretch of at least about 30
25 nucleotides to a primate DTLR5. Preferably, such nucleic
acid will have such properties, wherein: wash conditions
are at 45° C and/or 500 mM salt; or the identity is at
least 90% and/or the stretch is at least 55 nucleotides.

More preferably, the wash conditions are at 55° C
30 and/or 150 mM salt; or the identity is at least 95% and/or
the stretch is at least 75 nucleotides.

Also provided are methods of producing a
ligand:receptor complex, comprising contacting a
substantially pure primate DTLR2, DTLR3, DTLR4, DTLR5,
35 DTLR6, DTLR7, DTLR8, DTLR9, or DTLR10, including a
recombinant or synthetically produced protein, with

candidate Toll ligand; thereby allowing said complex to form.

The invention also provides a method of modulating physiology or development of a cell or tissue culture
5 cells comprising contacting the cell with an agonist or antagonist of a mammalian DTLR2, DTLR3, DTLR4, DTLR5, DTLR6, DTLR7, DTLR8, DTLR9, or DTLR10. Preferably, the cell is a pDC2 cell with the agonist or antagonist of DTLR10.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

OUTLINE

- I. General
- 5 II. Activities
- III. Nucleic acids
 - A. encoding fragments, sequence, probes
 - B. mutations, chimeras, fusions
 - C. making nucleic acids
 - 10 D. vectors, cells comprising
- IV. Proteins, Peptides
 - A. fragments, sequence, immunogens, antigens
 - B. muteins
 - C. agonists/antagonists, functional equivalents
 - 15 D. making proteins
- V. Making nucleic acids, proteins
 - A. synthetic
 - B. recombinant
 - C. natural sources
 - 20 VI. Antibodies
 - A. polyclonals
 - B. monoclonal
 - C. fragments; Kd
 - D. anti-idiotypic antibodies
 - 25 E. hybridoma cell lines
- VII. Kits and Methods to quantify DTLRs 2-10
 - A. ELISA
 - B. assay mRNA encoding
 - C. qualitative/quantitative
 - 30 D. kits
- VIII. Therapeutic compositions, methods
 - A. combination compositions
 - B. unit dose
 - C. administration
 - 35 IX. Ligands

I. General

The present invention provides the amino acid sequence and DNA sequence of mammalian, herein primate

40 DNAX Toll like receptor molecules (DTLR) having particular defined properties, both structural and biological. These have been designated herein as DTLR2, DTLR3, DTLR4, DTLR5, DTLR6, DTLR7, DTLR8, DTLR9, and DTLR10, respectively, and increase the number of members of the human Toll like

receptor family from 1 to 10. Various cDNAs encoding these molecules were obtained from primate, e.g., human, cDNA sequence libraries. Other primate or other mammalian counterparts would also be desired.

- 5 Some of the standard methods applicable are described or referenced, e.g., in Maniatis, et al. (1982) Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Laboratory, Cold Spring Harbor Press; Sambrook, et al. (1989) Molecular Cloning: A Laboratory Manual, (2d ed.), 10 vols. 1-3, CSH Press, NY; Ausubel, et al., Biology, Greene Publishing Associates, Brooklyn, NY; or Ausubel, et al. (1987 and periodic supplements) Current Protocols in Molecular Biology, Greene/Wiley, New York; each of which is incorporated herein by reference.
- 15 A complete nucleotide (SEQ ID NO: 1) and corresponding amino acid sequence (SEQ ID NO: 2) of a human DTLR1 coding segment is shown in Table 1. See also Nomura, et al. (1994) DNA Res. 1:27-35. A complete nucleotide (SEQ ID NO: 3) and corresponding amino acid 20 sequence (SEQ ID NO: 4) of a human DTLR2 coding segment is shown in Table 2. A complete nucleotide (SEQ ID NO: 5) and corresponding amino acid sequence (SEQ ID NO: 6) of a human DTLR3 coding segment is shown in Table 3. A complete nucleotide (SEQ ID NO: 7) and corresponding amino 25 acid sequence (SEQ ID NO: 8) of a human DTLR4 coding segment is shown in Table 4; see also SEQ ID NO: 25 and 26. A partial nucleotide (SEQ ID NO: 9) and corresponding amino acid sequence (SEQ ID NO: 10) of a human DTLR5 coding segment is shown in Table 5. A complete nucleotide 30 (SEQ ID NO: 11) and corresponding amino acid sequence (SEQ ID NO: 12) of a human DTLR6 coding segment is shown in Table 6, along with partial sequence of a mouse DTLR6 (SEQ ID NO: 13, 14, 27, 28, 29, and 30). Partial nucleotide (SEQ ID NO: 15 and 17) and corresponding amino acid 35 sequence (SEQ ID NO: 16 and 18) of a human DTLR7 coding segment is shown in Table 7; full length sequence is

provided in SEQ ID NO: 36 and 37. Partial nucleotide (SEQ ID NO: 19) and corresponding amino acid sequence (SEQ ID NO: 20) of a human DTLR8 coding segment is shown in Table 8, with supplementary sequence (SEQ ID NO: 31, 32, 38, and 39). Partial nucleotide (SEQ ID NO: 21) and corresponding amino acid sequence (SEQ ID NO: 22) of a human DTLR9 coding segment is shown in Table 9; see also SEQ ID NO: 40 and 41. Partial nucleotide (SEQ ID NO: 23) and corresponding amino acid sequence (SEQ ID NO: 24) of a human DTLR10 coding segment is shown in Table 10, along with supplementary sequence (SEQ ID NO: 33, 34, 42, and 43) and rodent, e.g., mouse, sequence (SEQ ID NO: 35, 44, and 45).

Table 1: Nucleotide and amino acid sequences (see SEQ ID NO: 1 and 2) of a primate, e.g., human, DNAX Toll like receptor 1 (DILR1).

5	ATG ACT AGC ATC TTC CAT TTT GCC ATT ATC TTC ATG TTA ATA CTT CAG Met Thr Ser Ile Phe His Phe Ala Ile Ile Phe Met Leu Ile Leu Gln -22 -20 -15 -10	48
10	ATC AGA ATA CAA TTA TCT GAA GAA AGT GAA TTT TTA GTT GAT AGG TCA Ile Arg Ile Gln Leu Ser Glu Glu Ser Glu Phe Leu Val Asp Arg Ser -5 1 5 10	96
15	AAA AAC GGT CTC ATC CAC GTT CCT AAA GAC CTA TCC CAG AAA ACA ACA Lys Asn Gly Leu Ile His Val Pro Lys Asp Leu Ser Gln Lys Thr Thr 15 20 25	144
20	ATC TTA AAT ATA TCG CAA AAT TAT ATA TCT GAG CTT TGG ACT TCT GAC Ile Leu Asn Ile Ser Gln Asn Tyr Ile Ser Glu Leu Trp Thr Ser Asp 30 35 40	192
25	ATC TTA TCA CTG TCA AAA CTG AGG ATT TTG ATA ATT TCT CAT AAT AGA Ile Leu Ser Leu Ser Lys Leu Arg Ile Leu Ile Ile Ser His Asn Arg 45 50 55	240
30	ATC CAG TAT CTT GAT ATC AGT GTT TTC AAA TTC AAC CAG GAA TTG GAA Ile Gln Tyr Leu Asp Ile Ser Val Phe Lys Phe Asn Gln Glu Leu Glu 60 65 70	288
35	TAC TTG GAT TTG TCC CAC AAC AAG TTG GTG AAG ATT TCT TGC CAC CCT Tyr Leu Asp Leu Ser His Asn Lys Leu Val Lys Ile Ser Cys His Pro 75 80 85 90	336
40	ACT GTG AAC CTC AAG CAC TTG GAC CTG TCA TTT AAT GCA TTT GAT GCC Thr Val Asn Leu Lys His Leu Asp Leu Ser Phe Asn Ala Phe Asp Ala 95 100 105	384
45	CTG CCT ATA TGC AAA GAG TTT GGC AAT ATG TCT CAA CTA AAA TTT CTG Leu Pro Ile Cys Lys Glu Phe Gly Asn Met Ser Gln Leu Lys Phe Leu 110 115 120	432
50	GGG TTG AGC ACC ACA CAC TTA GAA AAA TCT AGT GTG CTG CCA ATT GCT Gly Leu Ser Thr Thr His Leu Glu Lys Ser Ser Val Leu Pro Ile Ala 125 130 135	480
55	CAT TTG AAT ATC AGC AAG GTC TTG CTG GTC TTA GGA GAG ACT TAT GGG His Leu Asn Ile Ser Lys Val Leu Leu Val Leu Gly Glu Thr Tyr Gly 140 145 150	528
60	GAA AAA GAA GAC CCT GAG GGC CTT CAA GAC TTT AAC ACT GAG AGT CTG Glu Lys Glu Asp Pro Glu Gly Leu Gln Asp Phe Asn Thr Glu Ser Leu 155 160 165 170	576
65	CAC ATT GTG TTC CCC ACA AAC AAA GAA TTC CAT TTT ATT TTG GAT GTG His Ile Val Phe Pro Thr Asn Lys Glu Phe His Phe Ile Leu Asp Val 175 180 185	624

	TCA GTC AAG ACT GTA GCA AAT CTG GAA CTA TCT AAT ATC AAA TGT GTG Ser Val Lys Thr Val Ala Asn Leu Glu Leu Ser Asn Ile Lys Cys Val	672
	190 195 200	
5	CTA GAA GAT AAC AAA TGT TCT TAC TTC CTA AGT ATT CTG GCG AAA CTT Leu Glu Asp Asn Lys Cys Ser Tyr Phe Leu Ser Ile Leu Ala Lys Leu	720
	205 210 215	
10	CAA ACA AAT CCA AAG TTA TCA AGT CTT ACC TTA AAC AAC ATT GAA ACA Gln Thr Asn Pro Lys Leu Ser Ser Leu Thr Leu Asn Asn Ile Glu Thr	768
	220 225 230	
15	ACT TGG AAT TCT TTC ATT AGG ATC CTC CAA CTA GTT TGG CAT ACA ACT Thr Trp Asn Ser Phe Ile Arg Ile Leu Gln Leu Val Trp His Thr Thr	816
	235 240 245 250	
20	GTA TGG TAT TTC TCA ATT TCA AAC GTG AAG CTA CAG GGT CAG CTG GAC Val Trp Tyr Phe Ser Ile Ser Asn Val Lys Leu Gln Gly Gln Leu Asp	864
	255 260 265	
	TTC AGA GAT TTT GAT TAT TCT GGC ACT TCC TTG AAG GCC TTG TCT ATA Phe Arg Asp Phe Asp Tyr Ser Gly Thr Ser Leu Lys Ala Leu Ser Ile	912
	270 275 280	
25	CAC CAA GTT GTC AGC GAT GTG TTC GGT TTT CCG CAA AGT TAT ATC TAT His Gln Val Val Ser Asp Val Phe Gly Phe Pro Gln Ser Tyr Ile Tyr	960
	285 290 295	
30	GAA ATC TTT TCG AAT ATG AAC ATC AAA AAT TTC ACA GTG TCT GGT ACA Glu Ile Phe Ser Asn Met Asn Ile Lys Asn Phe Thr Val Ser Gly Thr	1008
	300 305 310	
35	CGC ATG GTC CAC ATG CTT TGC CCA TCC AAA ATT AGC CCG TTC CTG CAT Arg Met Val His Met Leu Cys Pro Ser Lys Ile Ser Pro Phe Leu His	1056
	315 320 325 330	
40	TTG GAT TTT TCC AAT AAT CTC TTA ACA GAC ACG GTT TTT GAA AAT TGT Leu Asp Phe Ser Asn Asn Leu Leu Thr Asp Thr Val Phe Glu Asn Cys	1104
	335 340 345	
	GGG CAC CTT ACT GAG TTG GAG ACA CTT ATT TTA CAA ATG AAT CAA TTA Gly His Leu Thr Glu Leu Glu Thr Leu Ile Leu Gln Met Asn Gln Leu	1152
	350 355 360	
45	AAA GAA CTT TCA AAA ATA GCT GAA ATG ACT ACA CAG ATG AAG TCT CTG Lys Glu Leu Ser Lys Ile Ala Glu Met Thr Thr Gln Met Lys Ser Leu	1200
	365 370 375	
50	CAA CAA TTG GAT ATT AGC CAG AAT TCT GTA AGC TAT GAT GAA AAG AAA Gln Gln Leu Asp Ile Ser Gln Asn Ser Val Ser Tyr Asp Glu Lys Lys	1248
	380 385 390	
55	GGA GAC TGT TCT TGG ACT AAA AGT TTA TTA AGT TTA AAT ATG TCT TCA Gly Asp Cys Ser Trp Thr Lys Ser Leu Leu Ser Leu Asn Met Ser Ser	1296
	395 400 405 410	

	AAT ATA CTT ACT GAC ACT ATT TTC AGA TGT TTA CCT CCC AGG ATC AAG	1344
	Asn Ile Leu Thr Asp Thr Ile Phe Arg Cys Leu Pro Pro Arg Ile Lys	
	415 420 425	
5	GTA CTT GAT CTT CAC AGC AAT AAA ATA AAG AGC ATT CCT AAA CAA GTC	1392
	Val Leu Asp Leu His Ser Asn Lys Ile Lys Ser Ile Pro Lys Gln Val	
	430 435 440	
10	GTA AAA CTG GAA GCT TTG CAA GAA CTC AAT GTT GCT TTC AAT TCT TTA	1440
	Val Lys Leu Glu Ala Leu Gln Glu Leu Asn Val Ala Phe Asn Ser Leu	
	445 450 455	
15	ACT GAC CTT CCT GCA TGT GGC AGC TTT AGC AGC CTT TCT GTA TTG ATC	1488
	Thr Asp Leu Pro Gly Cys Gly Ser Phe Ser Ser Leu Ser Val Leu Ile	
	460 465 470	
20	ATT GAT CAC AAT TCA GTT TCC CAC CCA TCA GCT GAT TTC TTC CAG AGC	1536
	Ile Asp His Asn Ser Val Ser His Pro Ser Ala Asp Phe Phe Gln Ser	
	475 480 485 490	
25	TGC CAG AAG ATG AGG TCA ATA AAA GCA GGG GAC AAT CCA TTC CAA TGT	1584
	Cys Gln Lys Met Arg Ser Ile Lys Ala Gly Asp Asn Pro Phe Gln Cys	
	495 500 505	
30	ACC TGT GAG CTC GGA GAA TTT GTC AAA AAT ATA GAC CAA GTA TCA AGT	1632
	Thr Cys Glu Leu Gly Glu Phe Val Lys Asn Ile Asp Gln Val Ser Ser	
	510 515 520	
35	GAA GTG TTA GAG GGC TGG CCT GAT TCT TAT AAG TGT GAC TAC CCG GAA	1680
	Glu Val Leu Glu Gly Trp Pro Asp Ser Tyr Lys Cys Asp Tyr Pro Glu	
	525 530 535	
40	AGT TAT AGA GGA ACC CTA CTA AAG GAC TTT CAC ATG TCT GAA TTA TCC	1728
	Ser Tyr Arg Gly Thr Leu Leu Lys Asp Phe His Met Ser Glu Leu Ser	
	540 545 550	
45	TGC AAC ATA ACT CTG CTG ATC GTC ACC ATC GTT GCC ACC ATG CTG GTG	1776
	Cys Asn Ile Thr Leu Leu Ile Val Thr Ile Val Ala Thr Met Leu Val	
	555 560 565 570	
50	TTG GCT GTG ACT GTG ACC TCC CTC TGC ATC TAC TTG GAT CTG CCC TGG	1824
	Leu Ala Val Thr Val Thr Ser Leu Cys Ile Tyr Leu Asp Leu Pro Trp	
	575 580 585	
55	TAT CTC AGG ATG GTG TGC CAG TGG ACC CAG ACC CGG CGC AGG GCC AGG	1872
	Tyr Leu Arg Met Val Cys Gln Trp Thr Gln Thr Arg Arg Arg Ala Arg	
	590 595 600	
60	AAC ATA CCC TTA GAA GAA CTC CAA AGA AAT CTC CAG TTT CAT GCA TTT	1920
	Asn Ile Pro Leu Glu Glu Leu Gln Arg Asn Leu Gln Phe His Ala Phe	
	605 610 615	

	ATT TCA TAT AGT GGG CAC GAT TCT TTC TGG GTG AAG AAT GAA TTA TTG	1966
	Ile Ser Tyr Ser Gly His Asp Ser Phe Trp Val Lys Asn Glu Leu Leu	
	620 625 630	
5	CCA AAC CTA GAG AAA GAA GGT ATG CAG ATT TGC CTT CAT GAG AGA AAC	2016
	Pro Asn Leu Glu Lys Glu Gly Met Gln Ile Cys Leu His Glu Arg Asn	
	635 640 645 650	
10	TTT GTT CCT GGC AAG AGC ATT GTG GAA AAT ATC ATC ACC TGC ATT GAG	2064
	Phe Val Pro Gly Lys Ser Ile Val Glu Asn Ile Ile Thr Cys Ile Glu	
	655 660 665	
15	AAG AGT TAC AAG TCC ATC TTT GTT TTG TCT CCC AAC TTT GTC CAG AGT	2112
	Lys Ser Tyr Lys Ser Ile Phe Val Leu Ser Pro Asn Phe Val Gln Ser	
	670 675 680	
20	GAA TGG TGC CAT TAT GAA CTC TAC TTT GCC CAT CAC AAT CTC TTT CAT	2160
	Glu Trp Cys His Tyr Glu Leu Tyr Phe Ala His His Asn Leu Phe His	
	685 690 695	
	GAA GGA TCT AAT AGC TTA ATC CTG ATC TTG CTG GAA CCC ATT CCG CAG	2208
	Glu Gly Ser Asn Ser Leu Ile Leu Ile Leu Leu Glu Pro Ile Pro Gln	
	700 705 710	
25	TAC TCC ATT CCT AGC AGT TAT CAC AAG CTC AAA AGT CTC ATG GCC AGG	2256
	Tyr Ser Ile Pro Ser Ser Tyr His Lys Leu Lys Ser Leu Met Ala Arg	
	715 720 725 730	
30	AGG ACT TAT TTG GAA TGG CCC AAG GAA AAG AGC AAA CGT GGC CTT TTT	2304
	Arg Thr Tyr Leu Glu Trp Pro Lys Glu Lys Ser Lys Arg Gly Leu Phe	
	735 740 745	
35	TGG GCT AAC TTA AGG GCA GCC ATT AAT ATT AAG CTG ACA GAG CAA GCA	2352
	Trp Ala Asn Leu Arg Ala Ala Ile Asn Ile Lys Leu Thr Glu Gln Ala	
	750 755 760	
	AAG AAA TAGTCTAGA	2367
	Lys Lys	
40	MTSIPHFAIIFMLILQIRIQLSESEFLVDRSKNGLIHVPKDLSQKTTILNISQNYISELWTS	
	ISHNRIQYLDISVFKFNQELEVLDSHNKLVKISCHPTVNLKHLDFSNAFDALPICKEFGNMSQLKFLGLSTTH	
	LEKSSVLPPIAHLNISKVLLVLGETYGEKEDPEGLQDFNTESLHIVFPTNKEFHFI	
	EDNKCSYFLSILAKLQTNPKLSSLTLNNIETWNSFIRILQLVWHTTVWYFSISNVKLQ	
45	ALSIHQVVSDFGFPQSYIYEIFSNMNIKNFTVSGTRMVHMLCPSKISPPHLDFSNNLLTDTVF	
	TLILQMNQLKELSKIAEMTTQMSLQQLDISQNSVSYDEKKGDCSWTKSLLSLNMSSN	
	DLESNKIKSIPKQVVKLEALQELNVAFNSLTDLPGCGSFSSLSVLIIDENSVSHP	
	FQCTCELGEFVKNIQVSSEVLEGWPDSYKCDYPESYRGTLTKDFHMSSELSCNITLLIVTIVATMLVLAVT	
	CIYLDLPWYLRMVCQWTQTRRRARNIPLEELQRNLQFHA FISYSGHDSFWVKNELLPNLEK	
50	GKSIVENIITCIEKSYKSIFVLSPNFVQSEWCHYEYFAHHNLFHEGSNSLILILLEPI	
	ARRTYLEWPKEKSKRGLFWANLRAAINIKLTEQAKK	

Table 2: Nucleotide and amino acid sequences (see SEQ ID NO: 3 and 4) of a primate, e.g., human, DNAX Toll like Receptor 2 (DTLR2).

5	ATG CCA CAT ACT TTG TGG ATG GTG TGG GTC TTG GGG GTC ATC ATC AGC	48
	Met Pro His Thr Leu Trp Met Val Trp Val Leu Gly Val Ile Ile Ser	
	-22 -20 -15 -10	
10	CTC TCC AAG GAA GAA TCC TCC AAT CAG GCT TCT CTG TCT TGT GAC CGC	96
	Leu Ser Lys Glu Glu Ser Ser Asn Gln Ala Ser Leu Ser Cys Asp Arg	
	-5 1 5 10	
15	AAT GGT ATC TGC AAG GGC AGC TCA GGA TCT TTA AAC TCC ATT CCC TCA	144
	Asn Gly Ile Cys Lys Gly Ser Ser Gly Ser Leu Asn Ser Ile Pro Ser	
	15 20 25	
20	GGG CTC ACA GAA GCT GTA AAA AGC CTT GAC CTG TCC AAC AAC AGG ATC	192
	Gly Leu Thr Glu Ala Val Lys Ser Leu Asp Leu Ser Asn Asn Arg Ile	
	30 35 40	
25	ACC TAC ATT AGC AAC AGT GAC CTA CAG AGG TGT GTG AAC CTC CAG GCT	240
	Thr Tyr Ile Ser Asn Ser Asp Leu Gln Arg Cys Val Asn Leu Gln Ala	
	45 50 55	
30	CTG GTG CTG ACA TCC AAT GGA ATT AAC ACA ATA GAG GAA GAT TCT TTT	288
	Leu Val Leu Thr Ser Asn Gly Ile Asn Thr Ile Glu Glu Asp Ser Phe	
	60 65 70	
35	TCT TCC CTG GGC AGT CTT GAA CAT TTA GAC TTA TCC TAT AAT TAC TTA	336
	Ser Ser Leu Gly Ser Leu Glu His Leu Asp Leu Ser Tyr Asn Tyr Leu	
	75 80 85 90	
40	TCT AAT TTA TCG TCT TCC TGG TTC AAG CCC CTT TCT TCT TTA ACA TTC	384
	Ser Asn Leu Ser Ser Ser Trp Phe Lys Pro Leu Ser Ser Leu Thr Phe	
	95 100 105	
45	TTA AAC TTA CTG GGA AAT CCT TAC AAA ACC CTA GGG GAA ACA TCT CTT	432
	Leu Asn Leu Leu Gly Asn Pro Tyr Lys Thr Leu Gly Glu Thr Ser Leu	
	110 115 120	
50	TTT TCT CAT CTC ACA AAA TTG CAA ATC CTG AGA GTG GGA AAT ATG GAC	480
	Phe Ser His Leu Thr Lys Leu Gln Ile Leu Arg Val Gly Asn Met Asp	
	125 130 135	
55	ACC TTC ACT AAG ATT CAA AGA AAA GAT TTT GCT GGA CTT ACC TTC CTT	528
	Thr Phe Thr Lys Ile Gln Arg Lys Asp Phe Ala Gly Leu Thr Phe Leu	
	140 145 150	
60	GAG GAA CTT GAG ATT GAT GCT TCA GAT CTA CAG AGC TAT GAG CCA AAA	576
	Glu Glu Leu Glu Ile Asp Ala Ser Asp Leu Gln Ser Tyr Glu Pro Lys	
	155 160 165 170	
65	AGT TTG AAG TCA ATT CAG AAC GTA AGT CAT CTG ATC CTT CAT ATG AAG	624
	Ser Leu Lys Ser Ile Gln Asn Val Ser His Leu Ile Leu His Met Lys	
	175 180 185	

	CAG CAT ATT TTA CTG CTG GAG ATT TTT GTA GAT GTT ACA AGT TCC GTG	672
	Gln His Ile Leu Leu Leu Glu Ile Phe Val Asp Val Thr Ser Ser Val	
	190 195 200	
5	GAA TGT TTG GAA CTG CGA GAT ACT GAT TTG GAC ACT TTC CAT TTT TCA	720
	Glu Cys Leu Glu Leu Arg Asp Thr Asp Leu Asp Thr Phe His Phe Ser	
	205 210 215	
10	GAA CTA TCC ACT GGT GAA ACA AAT TCA TTG ATT AAA AAG TTT ACA TTT	768
	Glu Leu Ser Thr Gly Glu Thr Asn Ser Leu Ile Lys Lys Phe Thr Phe	
	220 225 230	
15	AGA AAT GTG AAA ATC ACC GAT GAA AGT TTG TTT CAG GTT ATG AAA CTT	816
	Arg Asn Val Lys Ile Thr Asp Glu Ser Leu Phe Gln Val Met Lys Leu	
	235 240 245 250	
20	TTG AAT CAG ATT TCT GGA CTG TTA GAA TTA GAG TTT GAT GAC TGT ACC	864
	Leu Asn Gln Ile Ser Gly Leu Leu Glu Leu Glu Phe Asp Asp Cys Thr	
	255 260 265	
	CTT AAT GGA GTT GGT AAT TTT AGA GCA TCT GAT AAT GAC AGA GTT ATA	912
	Leu Asn Gly Val Gly Asn Phe Arg Ala Ser Asp Asn Asp Arg Val Ile	
	270 275 280	
25	GAT CCA GGT AAA GTG GAA ACG TTA ACA ATC CGG AGG CTG CAT ATT CCA	960
	Asp Pro Gly Lys Val Glu Thr Leu Thr Ile Arg Arg Leu His Ile Pro	
	285 290 295	
30	AGG TTT TAC TTA TTT TAT GAT CTG AGC ACT TTA TAT TCA CTT ACA GAA	1008
	Arg Phe Tyr Leu Phe Tyr Asp Leu Ser Thr Leu Tyr Ser Leu Thr Glu	
	300 305 310	
35	AGA GTT AAA AGA ATC ACA GTA GAA AAC AGT AAA GTT TTT CTG GTT CCT	1056
	Arg Val Lys Arg Ile Thr Val Glu Asn Ser Lys Val Phe Leu Val Pro	
	315 320 325 330	
40	TGT TTA CTT TCA CAA CAT TTA AAA TCA TTA GAA TAC TTG GAT CTC AGT	1104
	Cys Leu Leu Ser Gln His Leu Lys Ser Leu Glu Tyr Leu Asp Leu Ser	
	335 340 345	
	GAA AAT TTG ATG GTT GAA GAA TAC TTG AAA AAT TCA GCC TGT GAG GAT	1152
	Glu Asn Leu Met Val Glu Glu Tyr Leu Lys Asn Ser Ala Cys Glu Asp	
	350 355 360	
45	GCC TGG CCC TCT CTA CAA ACT TTA ATT TTA AGG CAA AAT CAT TTG GCA	1200
	Ala Trp Pro Ser Leu Gln Thr Leu Ile Leu Arg Gln Asn His Leu Ala	
	365 370 375	
50	TCA TIG GAA AAA ACC GGA GAG ACT TTG CTC ACT CTG AAA AAC TTG ACT	1248
	Ser Leu Glu Lys Thr Gly Glu Thr Leu Leu Thr Leu Lys Asn Leu Thr	
	380 385 390	
55	AAC ATT GAT ATC AGT AAG AAT AGT TTT CAT TCT ATG CCT GAA ACT TGT	1296
	Asn Ile Asp Ile Ser Lys Asn Ser Phe His Ser Met Pro Glu Thr Cys	
	395 400 405 410	

	CAG TGG CCA GAA AAG ATG AAA TAT TTG AAC TTA TCC AGC ACA CGA ATA	1344
	Gln Trp Pro Glu Lys Met Lys Tyr Leu Asn Leu Ser Ser Thr Arg Ile	
	415 420 425	
5	CAC AGT GTA ACA GGC TGC ATT CCC AAG ACA CTG GAA ATT TTA GAT GTT	1392
	His Ser Val Thr Gly Cys Ile Pro Lys Thr Leu Glu Ile Leu Asp Val	
	430 435 440	
10	AGC AAC AAC AAT CTC AAT TTA TTT TCT TTG AAT TTG CCG CAA CTC AAA	1440
	Ser Asn Asn Asn Leu Asn Leu Phe Ser Leu Asn Leu Pro Gln Leu Lys	
	445 450 455	
15	GAA CTT TAT ATT TCC AGA AAT AAG TTG ATG ACT CTA CCA GAT GCC TCC	1488
	Glu Leu Tyr Ile Ser Arg Asn Lys Leu Met Thr Leu Pro Asp Ala Ser	
	460 465 470	
20	CTC TTA CCC ATG TTA CTA GTA TTG AAA ATC AGT AGG AAT GCA ATA ACT	1536
	Leu Leu Pro Met Leu Leu Val Leu Lys Ile Ser Arg Asn Ala Ile Thr	
	475 480 485 490	
	ACG TTT TCT AAG GAG CAA CTT GAC TCA TTT CAC ACA CTG AAG ACT TTG	1584
	Thr Phe Ser Lys Glu Gln Leu Asp Ser Phe His Thr Leu Lys Thr Leu	
	495 500 505	
25	GAA GCT GGT GGC AAT AAC TTC ATT TGC TCC TGT GAA TTC CTC TCC TTC	1632
	Glu Ala Gly Gly Asn Asn Phe Ile Cys Ser Cys Glu Phe Leu Ser Phe	
	510 515 520	
30	ACT CAG GAG CAG CAA GCA CTG GCC AAA GTC TTG ATT GAT TGG CCA GCA	1680
	Thr Gln Glu Gln Gln Ala Leu Ala Lys Val Leu Ile Asp Trp Pro Ala	
	525 530 535	
35	AAT TAC CTG TGT GAC TCT CCA TCC CAT GTG CGT GGC CAG CAG GTT CAG	1728
	Asn Tyr Leu Cys Asp Ser Pro Ser His Val Arg Gly Gln Gln Val Gln	
	540 545 550	
40	GAT GTC CGC CTC TCG GTG TCG GAA TGT CAC AGG ACA GCA CTG GTG TCT	1776
	Asp Val Arg Leu Ser Val Ser Glu Cys His Arg Thr Ala Leu Val Ser	
	555 560 565 570	
	GGC ATG TGC TGT GCT CTG TTC CTG CTG ATC CTG CTC ACG GGC GTC CTG	1824
	Gly Met Cys Cys Ala Leu Phe Leu Leu Ile Leu Leu Thr Gly Val Leu	
	575 580 585	
45	TGC CAC CGT TTC CAT GGC CTG TGG TAT ATG AAA ATG ATG TGG GCC TGG	1872
	Cys His Arg Phe His Gly Leu Trp Tyr Met Lys Met Met Trp Ala Trp	
	590 595 600	
50	CTC CAG GCC AAA AGG AAG CCC AGG AAA GCT CCC AGC AGG AAC ATC TGC	1920
	Leu Gln Ala Lys Arg Lys Pro Arg Lys Ala Pro Ser Arg Asn Ile Cys	
	605 610 615	

	TAT GAT GCA TTT GTT TCT TAC AGT ZAG CGG GAT GCC TAC TGG GTG GAG	1958
	Tyr Asp Ala Phe Val Ser Tyr Ser Glu Arg Asp Ala Tyr Trp Val Glu	
	620 625 630	
5	AAC CTT ATG GTC CAG GAG CTG GAG AAC TTC AAT CCC CCC TTC AAG TTG	2016
	Asn Leu Met Val Gln Glu Leu Glu Asn Phe Asn Pro Pro Phe Lys Leu	
	635 640 645 650	
10	TGT CTT CAT AAG CGG GAC TTC ATT CCT GGC AAG TGG ATC ATT GAC AAT	2064
	Cys Leu His Lys Arg Asp Phe Ile Pro Gly Lys Trp Ile Ile Asp Asn	
	655 660 665	
15	ATC ATT GAC TCC ATT GAA AAG AGC CAC AAA ACT GTC TTT GTG CTT TCT	2112
	Ile Ile Asp Ser Ile Glu Lys Ser His Lys Thr Val Phe Val Leu Ser	
	670 675 680	
20	GAA AAC TTT GTG AAG AGT GAG TGG TGC AAG TAT GAA CTG GAC TTC TCC	2160
	Glu Asn Phe Val Lys Ser Glu Trp Cys Lys Tyr Glu Leu Asp Phe Ser	
	685 690 695	
25	CAT TTC CGT CTT TTT GAA GAG AAC AAT GAT GCT GCC ATT CTC ATT CTT	2208
	His Phe Arg Leu Phe Glu Glu Asn Asn Asp Ala Ala Ile Leu Ile Leu	
	700 705 710	
30	CTG GAG CCC ATT GAG AAA AAA GCC ATT CCC CAG CGC TTC TGC AAG CTG	2256
	Leu Glu Pro Ile Glu Lys Lys Ala Ile Pro Gln Arg Phe Cys Lys Leu	
	715 720 725 730	
35	CGG AAG ATA ATG AAC ACC AAG ACC TAC CTG GAG TGG CCC ATG GAC GAG	2304
	Arg Lys Ile Met Asn Thr Lys Thr Tyr Leu Glu Trp Pro Met Asp Glu	
	735 740 745	
40	GCT CAG CGG GAA GGA TTT TGG GTA AAT CTG AGA GCT GCG ATA AAG TCC	2352
	Ala Gln Arg Glu Gly Phe Trp Val Asn Leu Arg Ala Ala Ile Lys Ser	
	750 755 760	
	TAG	2355
45	MPHTLMVWVLGVILSLSKKESSNQASLSCDRNGICKSSSGSLNSIPSGLTEAVKSLDLSNNRITYISNSDLQRC	
	VNLQALVLTSGINTIEEDSFSSSLGSLHLDLSYNYLENLSSSWFKPLSSLTFLNLLGNPYKTLGETSLFSLTK	
	LQILRVGHMDTFTXIQRKDFAGLTFLELEIDASDLQSYBPKSLKSIQNVSHLILHMKOHILLLEIFVDVTSSVE	
	CLELRDLDLDTFHSELSTGETNSLIKKFTFRNVKITDESLPQVMKLLNQISGLLELEFDECTLNGVGNFRASDN	
	DRVIDPGKVETLTIRRLHIPRFYLFYDLSTLYSLTERVXRITVENSXVFLVPCLLSQHLKSLLEYLDLSENLMVEE	
	YLKNSACEDAWPSLQTLILRQNHLSLEXTGETLLTLKNLTNIDISKNSFHSMPEQCQNPEKMKYLNLSSTRIHS	
	VTGCIPTLEILDVSNNNLNLFSNLPPQLKELYISRNKMLTLPDASLLPMLLVLKISRNAITTFKSQQLDSPHTL	
	KCLEAGGNFICSCFELSTIQEQALAKVLIDWPANYLCDSPSHVRGQQVQDVRLSVSECHRTALVSGMCCALFL	
	LILLTGVLCHRFHGLWYMKMMWAWLQAKRKPRKAPSRNICYDAFVSYSERDAYWVENLMVQELENFNPPPKLCLH	
	KRDFIPGKWIIDNIIDSLEKSHKTVFVLSNFVKSEWCKYELDPSPRLFEENNDAAAILLEPIEKKAIPQRFC	
	KLRKIMNIKTYLEWPKDEAQRREGFWVNLRAATKS	

Table 3: Nucleotide and amino acid sequences (see SEQ ID NO: 5 and 6) of a mammalian, e.g., human, Toll like Receptor 3 (DTLR3).

5	ATG AGA CAG ACT TTG CCT TGT ATC TAC TTT TGG GGG GGC CTT TTG CCC Met Arg Gln Thr Leu Pro Cys Ile Tyr Phe Trp Gly Gly Leu Leu Pro -21 -20 -15 -10	48
10	TTT GGG ATG CTG TGT GCA TCC TCC ACC ACC AAG TGC ACT GTT AGC CAT Phe Gly Met Leu Cys Ala Ser Ser Thr Thr Lys Cys Thr Val Ser His -5 1 5 10	96
15	GAA GTT GCT GAC TGC AGC CAC CTG AAG TTG ACT CAG GTA CCC GAT GAT Glu Val Ala Asp Cys Ser His Leu Lys Leu Thr Gln Val Pro Asp Asp 15 20 25	144
20	CTA CCC ACA AAC ATA ACA GTG TTG AAC CTT ACC CAT AAT CAA CTC AGA Leu Pro Thr Asn Ile Thr Val Leu Asn Leu Thr His Asn Gln Leu Arg 30 35 40	192
25	AGA TTA CCA GCC GCC AAC TTC ACA AGG TAT AGC CAG CTA ACT AGC TTG Arg Leu Pro Ala Ala Asn Phe Thr Arg Tyr Ser Gln Leu Thr Ser Leu 45 50 55	240
30	GAT GTA GGA TTT AAC ACC ATC TCA AAA CTG GAG CCA GAA TTG TGC CAG Asp Val Gly Phe Asn Thr Ile Ser Lys Leu Glu Pro Glu Leu Cys Gln 60 65 70 75	288
35	AAA CTT CCC ATG TTA AAA GTT TTG AAC CTC CAG CAC AAT GAG CTA TCT Lys Leu Pro Met Leu Lys Val Leu Asn Leu Gln His Asn Glu Leu Ser 80 85 90	336
40	CAA CTT TCT GAT AAA ACC TTT GCC TTC TGC ACC AAT TTG ACT GAA CTC Gln Leu Ser Asp Lys Thr Phe Ala Phe Cys Thr Asn Leu Thr Glu Leu 95 100 105	384
45	CAT CTC ATG TCC AAC TCA ATC CAG AAA ATT AAA AAT AAT CCC TTT GTC His Leu Met Ser Asn Ser Ile Gln Lys Ile Lys Asn Asn Pro Phe Val 110 115 120	432
50	AAG CAG AAG AAT TTA ATC ACA TTA GAT CTG TCT CAT AAT GGC TTG TCA Lys Gln Lys Asn Leu Ile Thr Leu Asp Leu Ser His Asn Gly Leu Ser 125 130 135	480
55	TCT ACA AAA TTA GGA ACT CAG GTT CAG CTG GAA AAT CTC CAA GAG CTT Ser Thr Lys Leu Gly Thr Gln Val Gln Leu Glu Asn Leu Gln Glu Leu 140 145 150 155	528
60	CTA TTA TCA AAC AAT AAA ATT CAA GCG CTA AAA AGT GAA GAA CTG GAT Leu Leu Ser Asn Asn Lys Ile Gln Ala Leu Lys Ser Glu Glu Leu Asp 160 165 170	576
65	ATC TTT GCC AAT TCA TCT TTA AAA AAA TTA GAG TTG TCA TCG AAT CAA Ile Phe Ala Asn Ser Ser Leu Lys Lys Leu Glu Leu Ser Ser Asn Gln 175 180 185	624

	ATT AAA GAG TTT TCT CCA GGG TGT TTT CAC GCA ATT GGA AGA TTA TTT	672
	Ile Lys Glu Phe Ser Pro Gly Cys Phe His Ala Ile Gly Arg Leu Phe	
	190 195 200	
5	GGC CTC TTT CTG AAC AAT GTC CAG CTG GGT CCC AGC CTT ACA GAG AAG	720
	Gly Leu Phe Leu Asn Asn Val Gln Leu Gly Pro Ser Leu Thr Glu Lys	
	205 210 215	
10	CTA TGT TTG GAA TTA GCA AAC ACA AGC ATT CGG AAT CTG TCT CTG AGT	768
	Leu Cys Leu Glu Leu Ala Asn Thr Ser Ile Arg Asn Leu Ser Leu Ser	
	220 225 230 235	
15	AAC AGC CAG CTG TCC ACC ACC AGC AAT ACA ACT TTC TTG GGA CTA AAG	816
	Asn Ser Gln Leu Ser Thr Thr Ser Asn Thr Thr Phe Leu Gly Leu Lys	
	240 245 250	
20	TGG ACA AAT CTC ACT ATG CTC GAT CTT TCC TAC AAC AAC TTA AAT GTG	864
	Trp Thr Asn Leu Thr Met Leu Asp Leu Ser Tyr Asn Asn Leu Asn Val	
	255 260 265	
25	GTT GGT AAC GAT TCC TTT GCT TGG CTT CCA CAA CTA GAA TAT TTC TTC	912
	Val Gly Asn Asp Ser Phe Ala Trp Leu Pro Gln Leu Glu Tyr Phe Phe	
	270 275 280	
30	CTA GAG TAT AAT AAT ATA CAG CAT TTG TTT TCT CAC TCT TTG CAC GGG	960
	Leu Glu Tyr Asn Asn Ile Gln His Leu Phe Ser His Ser Leu His Gly	
	285 290 295	
35	CTT TTC AAT GTG AGG TAC CTG AAT TTG AAA CGG TCT TTT ACT AAA CAA	1008
	Leu Phe Asn Val Arg Tyr Leu Asn Leu Lys Arg Ser Phe Thr Lys Gln	
	300 305 310 315	
40	AGT ATT TCC CTT GCC TCA CTC CCC AAG ATT GAT GAT TTT TCT TTT CAG	1056
	Ser Ile Ser Leu Ala Ser Leu Pro Lys Ile Asp Asp Phe Ser Phe Gln	
	320 325 330	
45	TGG CTA AAA TGT TTG GAG CAC CTT AAC ATG GAA GAT AAT GAT ATT CCA	1104
	Trp Leu Lys Cys Leu Glu His Leu Asn Met Glu Asp Asn Asp Ile Pro	
	335 340 345	
50	GGC ATA AAA AGC AAT ATG TTC ACA GGA TTG ATA AAC CTG AAA TAC TTA	1152
	Gly Ile Lys Ser Asn Met Phe Thr Gly Leu Ile Asn Leu Lys Tyr Leu	
	350 355 360	
55	AGT CTA TCC AAC TCC TTT ACA AGT TTG CGA ACT TTG ACA AAT GAA ACA	1200
	Ser Leu Ser Asn Ser Phe Thr Ser Leu Arg Thr Leu Thr Asn Glu Thr	
	365 370 375	
60	TTT GTA TCA CTT GCT CAT TCT CCC TTA CAC ATA CTC AAC CTA ACC AAG	1248
	Phe Val Ser Leu Ala His Ser Pro Leu His Ile Leu Asn Leu Thr Lys	
	380 385 390 395	
65	AAT AAA ATC TCA AAA ATA GAG AGT GAT GCT TTC TCT TGG TTG GGC CAC	1296
	Asn Lys Ile Ser Lys Ile Glu Ser Asp Ala Phe Ser Trp Leu Gly His	
	400 405 410	

5	CTA GAA GTA CTT GAC CTG GGC CTT AAT GAA ATT GGG CAA GAA CTC ACA	1344
	Leu Glu Val Leu Asp Leu Gly Leu Asn Glu Ile Gly Gln Glu Leu Thr	
	415 420 425	
	GGC CAG GAA TGG AGA GGT CTA GAA AAT ATT TTC GAA ATC TAT CTT TCC	1392
	Gly Gln Glu Trp Arg Gly Leu Glu Asn Ile Phe Glu Ile Tyr Leu Ser	
10	430 435 440	
	TAC AAC AAG TAC CTG CAG CTG ACT AGG AAC TCC TTT GCC TTG GTC CCA	1440
	Tyr Asn Lys Tyr Leu Gln Leu Thr Arg Asn Ser Phe Ala Leu Val Pro	
	445 450 455	
	AGC CTT CAA CGA CTG ATG CTC CGA ACG GTG GCC CTT AAA AAT GTG GAT	1488
15	Ser Leu Gln Arg Leu Met Leu Arg Arg Val Ala Leu Lys Asn Val Asp	
	460 465 470 475	
	AGC TCT CCT TCA CCA TTC CAG CCT CTT CGT AAC TTG ACC ATT CTG GAT	1536
	Ser Ser Pro Ser Pro Phe Gln Pro Leu Arg Asn Leu Thr Ile Leu Asp	
	480 485 490	
20	CTA AGC AAC AAC AAC ATA GCC AAC ATA AAT GAT GAC ATG TTG GAG GGT	1584
	Leu Ser Asn Asn Asn Ile Ala Asn Ile Asn Asp Asp Met Leu Glu Gly	
	495 500 505	
	CTT GAG AAA CTA GAA ATT CTC GAT TTG CAG CAT AAC AAC TTA GCA CGG	1632
	Leu Glu Lys Leu Glu Ile Leu Asp Leu Gln His Asn Asn Leu Ala Arg	
25	510 515 520	
	CTC TGG AAA CAC GCA AAC CCT GGT GGT CCC ATT TAT TTC CTA AAG GGT	1680
	Leu Trp Lys His Ala Asn Pro Gly Gly Pro Ile Tyr Phe Leu Lys Gly	
	525 530 535	
	CTG TCT CAC CTC CAC ATC CTT AAC TTG GAG TCC AAC GGC TTT GAC GAG	1728
30	Leu Ser His Leu His Ile Leu Asn Leu Glu Ser Asn Gly Phe Asp Glu	
	540 545 550 555	
	ATC CCA GTT GAG GTC TTC AAG GAT TTA TTT GAA CTA AAG ATC ATC GAT	1776
	Ile Pro Val Glu Val Phe Lys Asp Leu Phe Glu Leu Lys Ile Ile Asp	
	560 565 570	
35	TTA GGA TTG AAT AAT TTA AAC ACA CTT CCA GCA TCT GTC TTT AAT AAT	1824
	Leu Gly Leu Asn Asn Leu Asn Thr Leu Pro Ala Ser Val Phe Asn Asn	
	575 580 585	
	CAG GTG TCT CTA AAG TCA TTG AAC CTT CAG AAG AAT CTC ATA ACA TCC	1872
	Gln Val Ser Leu Lys Ser Leu Asn Leu Gln Lys Asn Leu Ile Thr Ser	
40	590 595 600	
	CTT GAG AAG AAG GTT TTC GGG CCA GCT TTC AGG AAC CTG ACT GAG TTA	1920
	Val Glu Lys Lys Val Phe Gly Pro Ala Phe Arg Asn Leu Thr Glu Leu	
	605 610 615	

	GAT ATG CGC TTT AAT CCC TTT GAT TGC ACG TGT GAA AGT AIT GCC TGG	1968
	Asp Met Arg Phe Asn Pro Phe Asp Cys Thr Cys Glu Ser Ile Ala Trp	
	620 625 630 635	
5	TTT GTT AAT TGG ATT AAC GAG ACC CAT ACC AAC ATC CCT GAG CTG TCA	2016
	Phe Val Asn Trp Ile Asn Glu Thr His Thr Asn Ile Pro Glu Leu Ser	
	640 645 650	
10	AGC CAC TAC CTT TGC AAC ACT CCA CCT CAC TAT CAT GGG TTC CCA GTG	2064
	Ser His Tyr Leu Cys Asn Thr Pro Pro His Tyr His Gly Phe Pro Val	
	655 660 665	
15	AGA CTT TTT GAT ACA TCA TCT TGC AAA GAC AGT GCC CCC TTT GAA CTC	2112
	Arg Leu Phe Asp Thr Ser Ser Cys Lys Asp Ser Ala Pro Phe Glu Leu	
	670 675 680	
20	TTT TTC ATG ATC AAT ACC AGT ATC CTG TTG ATT TTT ATC TTT ACT GTA	2160
	Phe Phe Met Ile Asn Thr Ser Ile Leu Leu Ile Phe Ile Phe Ile Val	
	685 690 695	
25	CTT CTC ATC CAC TTT GAG GGC TGG AGG ATA TCT TTT TAT TGG AAT GTT	2208
	Leu Leu Ile His Phe Glu Gly Trp Arg Ile Ser Phe Tyr Trp Asn Val	
	700 705 710 715	
30	TCA GTA CAT CGA GTT CTT GGT TTC AAA GAA ATA GAC AGA CAG ACA GAA	2256
	Ser Val His Arg Val Leu Gly Phe Lys Glu Ile Asp Arg Gln Thr Glu	
	720 725 730	
35	CAG TTT GAA TAT GCA GCA TAT ATA ATT CAT GCC TAT AAA GAT AAG GAT	2304
	Gln Phe Glu Tyr Ala Ala Tyr Ile Ile His Ala Tyr Lys Asp Lys Asp	
	735 740 745	
40	TGG GTC TGG GAA CAT TTC TCT TCA ATG GAA AAG GAA GAC CAA TCT CTC	2352
	Trp Val Trp Glu His Phe Ser Ser Met Glu Lys Glu Asp Gln Ser Leu	
	750 755 760	
45	AAA TTT TGT CTG GAA GAA AGG GAC TTT GAG GCG GGT GTT TTT GAA CTA	2400
	Lys Phe Cys Leu Glu Glu Arg Asp Phe Glu Ala Gly Val Phe Glu Leu	
	765 770 775	
50	GAA GCA ATT GTT AAC AGC ATC AAA AGA AGC AGA AAA ATT ATT TTT GTT	2448
	Glu Ala Ile Val Asn Ser Ile Lys Arg Ser Arg Lys Ile Ile Phe Val	
	780 785 790 795	
55	ATA ACA CAC CAT CTA TTA AAA GAC CCA TTA TGC AAA AGA TTC AAG GTA	2496
	Ile Thr His His Leu Leu Lys Asp Pro Leu Cys Lys Arg Phe Lys Val	
	800 805 810	
60	CAT CAT GCA GTT CAA CAA GCT ATT GAA CAA AAT CTG GAT TCC ATT ATA	2544
	His His Ala Val Gln Gln Ala Ile Glu Gln Asn Leu Asp Ser Ile Ile	
	815 820 825	
65	TTG GTT TTC CTT GAG GAG ATT CCA GAT TAT AAA CTG AAC CAT GCA CTC	2592
	Leu Val Phe Leu Glu Glu Ile Pro Asp Tyr Lys Leu Asn His Ala Leu	
	830 835 840	

TGT TTG CGA AGA GGA ATG TTT AAA TCT CAC TGC ATC TTG AAC TGG CCA 2640
 Cys Leu Arg Arg Gly Met Phe Lys Ser His Cys Ile Leu Asn Trp Pro
 845 850 855

5 GTT CAG AAA GAA CGG ATA GGT GCC TTT CGT CAT AAA TTG CAA GTA GCA 2688
 Val Gln Lys Glu Arg Ile Gly Ala Phe Arg His Lys Leu Gln Val Ala
 860 865 870 875

10 CTT GGA TCC AAA AAC TCT GTA CAT TAA 2715
 Leu Gly Ser Lys Asn Ser Val His
 880

15 MRQTLPCIYFWGGLLPFGMICASSTTKCTVSHEVADCSHLKLTQVPDOLPTNITVLNLTHNQLRRLPAANFTRY
 QLTSLDVGFNTISKLEPELCQKLPMLKVLNLQHNELSQLSDKTFACFTNLTELHLMNSIQKIKNNPFVKQKNLI
 TLDLSHNGLSSTKLGTQVQLENLQELLLSNNKIQAALKSEELDIFANSSLKKELESSNQIKEFSPGCFHAIGRLFG
 LFLMNVQLGPSLTEKLCLELANTSIRNLSLSNSQLSTTSNTTFLGLKWTNLTMLDLSYNNLNVVGNDSFAWLPQL
 EYFFLEYNNIQHLFSLHGLFNVRYLNLKRSFTKQSI SLASLPKIDDFSQWLKCLEHLNEMEDNDIPGIKSNMF
 TGLINLKYL SLSNSFTSLRTLNETFVSLAHSPLHILNLTKNKISKIESDAFSWLGCHLEVLDLGLNEIGQELTGO
 20 EWRGLENIFEIYLSYNKYQLTRNSFALVPSLQRLMLRRVALKNVDSSPSPFQPLRNLITLDLSNNNIANINDDM
 LEGLEKLEILDQLQHNNLARLWKHANPGGPYFLKGLSHLHILNLESNGFDEIPVEVFKDLFELKIIDLGLNNLNT
 LPASVFNNQVSLKSLNLQKNLITSVEKKVFGPAFRNLTELOMRFPFDCTCESIAWFVNWINETHTNIPELSSHY
 LCNTPPHYHGFPVRLFDTSCKDSAPFELFFMINTSILIFIFIVLLIHFEGWRI SFYWNVSVERVLGFKELDRQ
 TEQFEYAAYIIHAYKDKDWVWEHFSSMEKEDQSLKFCLEERDFEAGVFLEAIVNSIKRSRKII FVTHHLKDP
 25 LCKREKVVHNAVQQAIEQNLDSEILVFLEEIPDYKLNHALCLRRGMFKSHCILNWDVQKERIGAFRHKLQVALGSK
 NSVH

Table 4: Nucleotide and amino acid sequences (see SEQ ID NO: 7 and 8) of a mammalian, e.g., primate, human, DNAX Toll like Receptor 4 (DTLR4).

5	ATG GAG CTG AAT TTC TAC AAA ATC CCC GAC AAC CTC CCC TTC TCA ACC	48
	Met Glu Leu Asn Phe Tyr Lys Ile Pro Asp Asn Leu Pro Phe Ser Thr	
	1 5 10 15	
10	AAG AAC CTG GAC CTG AGC TTT AAT CCC CTG AGG CAT TTA GGC AGC TAT	96
	Lys Asn Leu Asp Leu Ser Phe Asn Pro Leu Arg His Leu Gly Ser Tyr	
	20 25 30	
15	AGC TTC TTC AGT TTC CCA GAA CTG CAG GTG CTG GAT TTA TCC AGG TGT	144
	Ser Phe Phe Ser Phe Pro Glu Leu Gln Val Leu Asp Leu Ser Arg Cys	
	35 40 45	
20	GAA ATC CAG ACA ATT GAA GAT GGG GCA TAT CAG AGC CTA AGC CAC CTC	192
	Glu Ile Gln Thr Ile Glu Asp Gly Ala Tyr Gln Ser Leu Ser His Leu	
	50 55 60	
25	TCT ACC TTA ATA TTG ACA GGA AAC CCC ATC CAG AGT TTA GCC CTG GGA	240
	Ser Thr Leu Ile Leu Thr Gly Asn Pro Ile Gln Ser Leu Ala Leu Gly	
	65 70 75 80	
30	GCC TTT TCT GGA CTA TCA AGT TTA CAG AAG CTG GTG GCT GTG GAG ACA	288
	Ala Phe Ser Gly Leu Ser Ser Leu Gln Lys Leu Val Ala Val Glu Thr	
	85 90 95	
35	AAT CTA GCA TCT CTA GAG AAC TTC CCC ATT GGA CAT CTC AAA ACT TTG	336
	Asn Leu Ala Ser Leu Glu Asn Phe Pro Ile Gly His Leu Lys Thr Leu	
	100 105 110	
40	AAA GAA CTT AAT GTG GCT CAC AAT CTT ATC CAA TCT TTC AAA TTA CCT	384
	Lys Glu Leu Asn Val Ala His Asn Leu Ile Gln Ser Phe Lys Leu Pro	
	115 120 125	
45	GAG TAT TTT TCT AAT CTG ACC AAT CTA GAG CAC TTG GAC CTT TCC AGC	432
	Glu Tyr Phe Ser Asn Leu Thr Asn Leu Glu His Leu Asp Leu Ser Ser	
	130 135 140	
50	AAC AAG ATT CAA AGT ATT TAT TGC ACA GAC TTG CGG GTT CTA CAT CAA	480
	Asn Lys Ile Gln Ser Ile Tyr Cys Thr Asp Leu Arg Val Leu His Gln	
	145 150 155 160	
55	ATG CCC CTA CTC AAT CTC TCT TTA GAC CTG TCC CTG AAC CCT ATG AAC	528
	Met Pro Leu Leu Asn Leu Ser Leu Asp Leu Ser Leu Asn Pro Met Asn	
	165 170 175	
60	TTT ATC CAA CCA GGT GCA TTT AAA GAA ATT AGG CTT CAT AAG CTG ACT	576
	Phe Ile Gln Pro Gly Ala Phe Lys Glu Ile Arg Leu His Lys Leu Thr	
	180 185 190	
65	TTA AGA AAT AAT TTT GAT AGT TTA AAT GAA ATG AAA ACT TGT ATT CAA	624
	Leu Arg Asn Asn Phe Asp Ser Leu Asn Val Met Lys Thr Cys Ile Gln	
	195 200 205	

	GGT CTG GCT GGT TTA GAA GTC CAT CGT TTG GTT CTG GGA GAA TTT AGA Gly Leu Ala Gly Leu Glu Val His Arg Leu Val Leu Gly Glu Phe Arg 210 215 220	672
5	AAT GAA GGA AAC TTG GAA AAG TTT GAC AAA TCT GCT CTA GAG GGC CTG Asn Glu Gly Asn Leu Glu Lys Phe Asp Lys Ser Ala Leu Glu Gly Leu 225 230 235 240	720
10	TGC AAT TTG ACC ATT GAA GAA TTC CGA TTA GCA TAC TTA GAC TAC TAC Cys Asn Leu Thr Ile Glu Glu Phe Arg Leu Ala Tyr Leu Asp Tyr Tyr 245 250 255	768
15	CTC GAT GAT ATT ATT GAC TTA TTT AAT TGT TTG ACA AAT GTT TCT TCA Leu Asp Asp Ile Ile Asp Leu Phe Asn Cys Leu Thr Asn Val Ser Ser 260 265 270	816
20	TTT TCC CTG GTG AGT GTG ACT ATT GAA AGG GTA AAA GAC TTT TCT TAT Phe Ser Leu Val Ser Val Thr Ile Glu Arg Val Lys Asp Phe Ser Tyr 275 280 285	864
	AAT TTC GGA TGG CAA CAT TTA GAA TTA GTT AAC TGT AAA TTT GGA CAG Asn Phe Gly Trp Gln His Leu Glu Leu Val Asn Cys Lys Phe Gly Gln 290 295 300	912
25	TTT CCC ACA TTG AAA CTC AAA TCT CTC AAA AGG CTT ACT TTC ACT TCC Phe Pro Thr Leu Lys Leu Lys Ser Leu Lys Arg Leu Thr Phe Thr Ser 305 310 315 320	960
30	AAC AAA GGT GGG AAT GCT TTT TCA GAA GTT GAT CTA CCA AGC CTT GAG Asn Lys Gly Gly Asn Ala Phe Ser Glu Val Asp Leu Pro Ser Leu Glu 325 330 335	1008
35	TTT CTA GAT CTC AGT AGA AAT GGC TTG AGT TTC AAA GGT TGC TGT TCT Phe Leu Asp Leu Ser Arg Asn Gly Leu Ser Phe Lys Gly Cys Cys Ser 340 345 350	1056
40	CAA AGT GAT TTT GGG ACA ACC AGC CTA AAG TAT TTA GAT CTG AGC TTC Gln Ser Asp Phe Gly Thr Thr Ser Leu Lys Tyr Leu Asp Leu Ser Phe 355 360 365	1104
	AAT GGT GTT ATT ACC ATG AGT TCA AAC TTC TTG GGC TTA GAA CAA CTA Asn Gly Val Ile Thr Met Ser Ser Asn Phe Leu Gly Leu Glu Gln Leu 370 375 380	1152
45	GAA CAT CTG GAT TTC CAG CAT TCC AAT TTG AAA CAA ATG AGT GAG TTT Glu His Leu Asp Phe Gln His Ser Asn Leu Lys Gln Met Ser Glu Phe 385 390 395 400	1200
50	TCA GTA TTC CTA TCA CTC AGA AAC CTC ATT TAC CTT GAC ATT TCT CAT Ser Val Phe Leu Ser Leu Arg Asn Leu Ile Tyr Leu Asp Ile Ser His 405 410 415	1248
55	ACT CAC ACC AGA GTT GCT TTC AAT GGC ATC TTC AAT GGC TTG TCC AGT Thr His Thr Arg Val Ala Phe Asn Gly Ile Phe Asn Gly Leu Ser Ser 420 425 430	1296

5	CTC GAA GTC TTG AAA ATG GCT GGC AAT TCT TTC CAG GAA AAC TTC CTT	1344
	Leu Glu Val Leu Lys Met Ala Gly Asn Ser Phe Gln Glu Asn Phe Leu	
	435 440 445	
10	CCA GAT ATC TTC ACA GAG CTG AGA AAC TTG ACC TTC CTG GAC CTC TCT	1392
	Pro Asp Ile Phe Thr Glu Leu Arg Asn Leu Thr Phe Leu Asp Leu Ser	
	450 455 460	
15	CAG TGT CAA CTG GAG CAG TTG TCT CCA ACA GCA TTT AAC TCA CTC TCC	1440
	Gln Cys Gln Leu Glu Gln Leu Ser Pro Thr Ala Phe Asn Ser Leu Ser	
	465 470 475 480	
20	AGT CTT CAG GTA CTA AAT ATG AGC CAC AAC AAC TTC TTT TCA TTG GAT	1488
	Ser Leu Gln Val Leu Asn Met Ser His Asn Asn Phe Phe Ser Leu Asp	
	485 490 495	
25	ACG TTT CCT TAT AAG TGT CTG AAC TCC CTC CAG GTT CTT GAT TAC AGT	1536
	Thr Phe Pro Tyr Lys Cys Leu Asn Ser Leu Gln Val Leu Asp Tyr Ser	
	500 505 510	
30	CTC AAT CAC ATA ATG ACT TCC AAA AAA CAG GAA CTA CAG CAT TTT CCA	1584
	Leu Asn His Ile Met Thr Ser Lys Lys Gln Glu Leu Gln His Phe Pro	
	515 520 525	
35	AGT AGT CTA GCT TTC TTA AAT CTT ACT CAG AAT GAC TTT GCT TGT ACT	1632
	Ser Ser Leu Ala Phe Leu Asn Leu Thr Gln Asn Asp Phe Ala Cys Thr	
	530 535 540	
40	TGT GAA CAC CAG AGT TTC CTG CAA TGG ATC AAG GAC CAG AGG CAG CTC	1680
	Cys Glu His Gln Ser Phe Leu Gln Trp Ile Lys Asp Gln Arg Gln Leu	
	545 550 555 560	
45	TTG GTG GAA GTT GAA CGA ATG GAA TGT GCA ACA CCT TCA GAT AAG CAG	1728
	Leu Val Glu Val Glu Arg Met Glu Cys Ala Thr Pro Ser Asp Lys Gln	
	565 570 575	
50	GGC ATG CCT GTG CTG AGT TTG AAT ATC ACC TGT CAG ATG AAT AAG ACC	1776
	Gly Met Pro Val Leu Ser Leu Asn Ile Thr Cys Gln Met Asn Lys Thr	
	580 585 590	
55	ATC ATT GGT GTG TCG GTC CTC AGT GTG CTT GTA GTA TCT GTT GTA GCA	1824
	Ile Ile Gly Val Ser Val Leu Ser Val Leu Val Val Ser Val Val Ala	
	595 600 605	
60	GTT CTG GTC TAT AAG TTC TAT TTT CAC CTG ATG CTT CTT GCT GGC TGC	1872
	Val Leu Val Tyr Lys Phe Tyr Phe His Leu Met Leu Leu Ala Gly Cys	
	610 615 620	
65	ATA AAG TAT GGT AGA GGT GAA AAC ATC TAT GAT GCC TTT GTT ATC TAC	1920
	Ile Lys Tyr Gly Arg Gly Glu Asn Ile Tyr Asp Ala Phe Val Ile Tyr	
	625 630 635 640	

	TCA AGC CAG GAT GAG GAC TGG GTA AGG AAT GAG CTA GTA AAG AAT TTA	1968
	Ser Ser Gln Asp Glu Asp Trp Val Arg Asn Glu Leu Val Lys Asn Leu	
	645 650 655	
5	GAA GAA GGG GTG CCT CCA TTT CAG CTC TGC CTT CAC TAC AGA GAC TTT	2016
	Glu Glu Gly Val Pro Pro Phe Gln Leu Cys Leu His Tyr Arg Asp Phe	
	660 665 670	
10	ATT CCC GGT GTG GCC ATT GCT GCC AAC ATC ATC CAT GAA GGT TTC CAT	2064
	Ile Pro Gly Val Ala Ile Ala Asn Ile Ile His Glu Gly Phe His	
	675 680 685	
15	AAA AGC CGA AAG GTG ATT GTT GTG GTG TCC CAG CAC TTC ATC CAG AGC	2112
	Lys Ser Arg Lys Val Ile Val Val Ser Gln His Phe Ile Gln Ser	
	690 695 700	
20	CGC TGG TGT ATC TTT GAA TAT GAG ATT GCT CAG ACC TGG CAG TTT CTG	2160
	Arg Trp Cys Ile Phe Glu Tyr Glu Ile Ala Gln Thr Trp Gln Phe Leu	
	705 710 715 720	
	AGC AGC CGT GCT GGT ATC ATC TTC ATT GTC CTG CAG AAG GTG GAG AAG	2208
	Ser Ser Arg Ala Gly Ile Ile Phe Ile Val Leu Gln Lys Val Glu Lys	
	725 730 735	
25	ACC CTG CTC AGG CAG CAG GTG GAG CTG TAC CGC CTT CTC AGC AGG AAC	2256
	Thr Leu Leu Arg Gln Gln Val Glu Leu Tyr Arg Leu Leu Ser Arg Asn	
	740 745 750	
30	ACT TAC CTG GAG TGG GAG GAC AGT GTC CTG GGG CGG CAC ATC TTC TGG	2304
	Thr Tyr Leu Glu Trp Glu Asp Ser Val Leu Gly Arg His Ile Phe Trp	
	755 760 765	
35	AGA CGA CTC AGA AAA GCC CTG CTG GAT GGT AAA TCA TGG AAT CCA GAA	2352
	Arg Arg Leu Arg Lys Ala Leu Leu Asp Gly Lys Ser Trp Asn Pro Glu	
	770 775 780	
40	GGA ACA GTG GGT ACA GGA TGC AAT TGG CAG GAA GCA ACA TCT ATC	2397
	Gly Thr Val Gly Thr Gly Cys Asn Trp Gln Glu Ala Thr Ser Ile	
	785 790 795	
	TGA	2400
45	MELNFKIPDNLPFSTKNLDLSFNPLRHLGSSYSFFSFPELQVLDLSRCEIQTIEDGAYQSLSHLSTLILTGNP	
	IQSLALGAFSGLSLQKLVAVETNLSLENFPIGHLKTLKELNVAHNLIQSFKLPEYFSNLTNLEHLDLSSNK	
	IQSIYCTDLRVLHQMPLLNLSLDLSLNPMMFJQPGAFFEIRLHKLTLRNNFDSLNVMTCTIQGLAGLEVHRLV	
	LGEFFRNEGNLEKFDKSALEGLCNLTIEEFRLAYLDYVLDDEIDLENCLTNVSSFSLSVSVTIERVKDFSYNFGW	
	QHLELVNCKFGQFPPTLKLKSLKRLTFTSNKGGNAFSEVDLPSEFLDLSRNGLSFKGCCSQSDFGTTSLKYLD	
	LSFNGVITMSSNFLGLEQLEHLDFOHSNLKQMSEFSVFLSLRNLIYLDISHTHTRVAFNGIFNGLSSLEVLKM	
	AGNSFQENFLPDIFTLRNLTFLDLSQCQLEQLSPTAFNSLSLQVLNMSHNNFFSLDTFPYKCLNSLOVLDY	
50	SLNHIMTSKKQELQHFPSLAFLNLTQNDFACTCEHQSFQWIKDQRLVEVERMECATPSDKQGMPLVLSLN	
	ITCQMNKTIIGSVLSVLVSVVAVLVYKFYFHLMLLAGCIKYGRSENIYDAFVIYSSQDEDWVRNELVKNLE	
	EGVPPFQLCLHYRDFIPGVAIAANIIHEGFHKSARKVIVVVSQHFQSRWCIFEYEIAQTWQFLSSRAGIIFIV	
	LQKVEKTLRQQVELYRLLSRNTYLEWEDSVLGRHIFWRRRLRKALLDGKSWNPEGTVGTGCNWQEATSI	

supplemented primate, e.g., human, DTLR4 sequence (SEQ ID NO: 25 and 26); note that nucleotides 81, 3144, 3205, and 3563 designated A, each may be A, C, G, or T; nucleotides 3132, 3532, 3538, and 3553 designated G, each may be G or T; nucleotide 3638 designated A, may be A or T; and nucleotides 3677, 3685, and 3736 designated C, each may be A or C:		
5	AAAATACTCC CTTGCTCAA AAACGTCTCG GTCAAACGGT GATAGCAAAC CACGCATTCA	60
10	CAGGGCCACT GCTGCTCACA AAACCACTGA GGATGATGCC AGGATG ATG TCT GCC Met Ser Ala -22 -20	115
15	TCG CGC CTG GCT GGG ACT CTG ATC CCA GCC ATG GCC TTC CTC TCC TGC Ser Arg Leu Ala Gly Thr Leu Ile Pro Ala Met Ala Phe Leu Ser Cys -15 -10 -5	163
20	GTG AGA CCA GAA AGC TGG GAG CCC TGC GTG GAG GTT CCT AAT ATT ACT Val Arg Pro Glu Ser Trp Glu Pro Cys Val Glu Val Pro Asn Ile Thr 1 5 10	211
25	TAT CAA TGC ATG GAG CTG AAT TTC TAC AAA ATC CCC GAC AAC CTC CCC Tyr Gln Cys Met Glu Leu Asn Phe Tyr Lys Ile Pro Asp Asn Leu Pro 15 20 25	259
30	TTC TCA ACC AAG AAC CTG GAC CTG AGC TTT AAT CCC CTG AGG CAT TTA Phe Ser Thr Lys Asn Leu Asp Leu Ser Phe Asn Pro Leu Arg His Leu 30 35 40 45	307
35	GGC AGC TAT AGC TTC TTC AGT TTC CCA GAA CTG CAG GTG CTC GAT TTA Gly Ser Tyr Ser Phe Phe Ser Phe Pro Glu Leu Gln Val Leu Asp Leu 50 55 60	355
40	TCC AGG TGT GAA ATC CAG ACA ATT GAA GAT GGG GCA TAT CAG AGC CTA Ser Arg Cys Glu Ile Gln Thr Ile Glu Asp Gly Ala Tyr Gln Ser Leu 65 70 75	403
45	AGC CAC CTC TCT ACC TTA ATA TTG ACA GGA AAC CCC ATC CAG AGT TTA Ser His Leu Ser Thr Leu Ile Leu Thr Gly Asn Pro Ile Gln Ser Leu 80 85 90	451
50	GCC CTG GGA GCC TTT TCT GGA CTA TCA AGT TTA CAG AAG CTG GTG GCT Ala Leu Gly Ala Phe Ser Gly Leu Ser Ser Leu Gln Lys Leu Val Ala 95 100 105	499
55	GTG GAG ACA AAT CTA GCA TCT CTA GAG AAC TTC CCC ATT GGA CAT CTC Val Glu Thr Asn Leu Ala Ser Leu Glu Asn Phe Pro Ile Gly His Leu 110 115 120 125	547
60	AAA ACT TTG AAA GAA CTT AAT GTG GCT CAC AAT CTT ATC CAA TCT TTC Lys Thr Leu Lys Glu Leu Asn Val Ala His Asn Leu Ile Gln Ser Phe 130 135 140	595
65	AAA TTA CCT GAG TAT TTT TCT AAT CTG ACC AAT CTA GAG CAC TTG GAC Lys Leu Pro Glu Tyr Phe Ser Asn Leu Thr Asn Leu Glu His Leu Asp 145 150 155	643

	CTT TCC AGC AAC AAG ATT CAA AGT ATT TAT TGC ACA GAC TTG CGG GTT	691
	Leu Ser Ser Asn Lys Ile Gln Ser Ile Tyr Cys Thr Asp Leu Arg Val	
	160 165 170	
5	CTA CAT CAA ATG CCC CTA CTC AAT CTC TCT TTA GAC CTG TCC CTG AAC	739
	Leu His Gln Met Pro Leu Leu Asn Leu Ser Leu Asp Leu Ser Leu Asn	
	175 180 185	
10	CCT ATG AAC TTT ATC CAA CCA GGT GCA TTT AAA GAA ATT AGG CTT CAT	787
	Pro Met Asn Phe Ile Gln Pro Gly Ala Phe Lys Glu Ile Arg Leu His	
	190 195 200 205	
15	AAG CTG ACT TTA AGA AAT AAT TTT GAT AGT TTA AAT GTA ATG AAA ACT	835
	Lys Leu Thr Leu Arg Asn Asn Phe Asp Ser Leu Asn Val Met Lys Thr	
	210 215 220	
20	TGT ATT CAA GGT CTC CCT GGT TTA GAA GTC CAT CGT TTG GTT CTG GGA	883
	Cys Ile Gln Gly Leu Ala Gly Leu Glu Val His Arg Leu Val Leu Gly	
	225 230 235	
	GAA TTT AGA AAT GAA GGA AAC TTG GAA AAG TTT GAC AAA TCT GCT CTA	931
	Glu Phe Arg Asn Glu Gly Asn Leu Glu Lys Phe Asp Lys Ser Ala Leu	
	240 245 250	
25	GAG GGC CTG TGC AAT TTG ACC ATT GAA GAA TTC CGA TTA GCA TAC TTA	979
	Glu Gly Leu Cys Asn Leu Thr Ile Glu Glu Phe Arg Leu Ala Tyr Leu	
	255 260 265	
30	GAC TAC TAC CTC GAT GAT ATT ATT GAC TTA TTT AAT TGT TTG ACA AAT	1027
	Asp Tyr Tyr Leu Asp Asp Ile Ile Asp Leu Phe Asn Cys Leu Thr Asn	
	270 275 280 285	
35	GTT TCT TCA TTT TCC CTG GTG AGT GTG ACT ATT GAA AGG GTA AAA GAC	1075
	Val Ser Ser Phe Ser Leu Val Ser Val Thr Ile Glu Arg Val Lys Asp	
	290 295 300	
40	TTT TCT TAT AAT TTC GGA TGG CAA CAT TTA GAA TTA GTT AAC TGT AAA	1123
	Phe Ser Tyr Asn Phe Gly Trp Gln His Leu Glu Leu Val Asn Cys Lys	
	305 310 315	
	TTT GGA CAG TTT CCC ACA TTG AAA CTC AAA TCT CTC AAA AGG CTT ACT	1171
	Phe Gly Gln Phe Pro Thr Leu Lys Leu Lys Ser Leu Lys Arg Leu Thr	
	320 325 330	
45	TTC ACT TCC AAC AAA GGT GGG AAT GCT TTT TCA GAA GTT GAT CTA CCA	1219
	Phe Thr Ser Asn Lys Gly Gly Asn Ala Phe Ser Glu Val Asp Leu Pro	
	335 340 345	
50	AGC CTT GAG TTT CTA GAT CTC AGT AGA AAT GGC TTG AGT TTC AAA GGT	1267
	Ser Leu Glu Phe Leu Asp Leu Ser Arg Asn Gly Leu Ser Phe Lys Gly	
	350 355 360 365	

	TGC TGT TCT CAA AGT GAT TTT GGG ACA ACC AGC CTA AAG TAT TTA GAT	1315
	Cys Cys Ser Gln Ser Asp Phe Gly Thr Thr Ser Leu Lys Tyr Leu Asp	
	370 375 380	
5	CTG AGC TTC AAT GGT GTT ATT ACC ATG AGT TCA AAC TTC TTG GGC TTA	1363
	Leu Ser Phe Asn Gly Val Ile Thr Met Ser Ser Asn Phe Leu Gly Leu	
	385 390 395	
10	GAA CAA CTA GAA CAT CTG GAT TTC CAG CAT TCC AAT TTG AAA CAA ATG	1411
	Glu Gln Leu Glu His Leu Asp Phe Gln His Ser Asn Leu Lys Gln Met	
	400 405 410	
15	AGT GAG TTT TCA GTA TTC CTA TCA CTC AGA AAC CTC ATT TAC CTT GAC	1459
	Ser Glu Phe Ser Val Phe Leu Ser Leu Arg Asn Leu Ile Tyr Leu Asp	
	415 420 425	
20	ATT TCT CAT ACT CAC ACC AGA GTT GCT TTC AAT GGC ATC TTC AAT GGC	1507
	Ile Ser His Thr His Thr Arg Val Ala Phe Asn Gly Ile Phe Asn Gly	
	430 435 440 445	
	TTG TCC AGT CTC GAA GTC TTG AAA ATG GCT GGC AAT TCT TTC CAG GAA	1555
	Leu Ser Ser Leu Glu Val Leu Lys Met Ala Gly Asn Ser Phe Gln Glu	
	450 455 460	
25	AAC TTC CTT CCA GAT ATC TTC ACA GAG CTG AGA AAC TTG ACC TTC CTG	1603
	Asn Phe Leu Pro Asp Ile Phe Thr Gln Leu Arg Asn Leu Thr Phe Leu	
	465 470 475	
30	GAC CTC TCT CAG TGT CAA CTG GAG CAG ITG TCT CCA ACA GCA TTT AAC	1651
	Asp Leu Ser Gln Cys Gln Leu Glu Gln Leu Ser Pro Thr Ala Phe Asn	
	480 485 490	
35	TCA CTC TCC AGT CTT CAG GTA CTA AAT ATG AGC CAC AAC AAC TTC TTT	1699
	Ser Leu Ser Ser Leu Gln Val Leu Asn Met Ser His Asn Asn Phe Phe	
	495 500 505	
40	TCA TTG GAT ACG TTT CCT TAT AAG TGT CTG AAC TCC CTC CAG GTT CTT	1747
	Ser Leu Asp Thr Phe Pro Tyr Lys Cys Leu Asn Ser Leu Gln Val Leu	
	510 515 520 525	
	GAT TAC AGT CTC AAT CAC ATA ATG ACT TCC AAA AAA CAG GAA CTA CAG	1795
	Asp Tyr Ser Leu Asn His Ile Met Thr Ser Lys Lys Gln Glu Leu Gln	
	530 535 540	
45	CAT TTT CCA AGT AGT CTA GCT TTC TTA AAT CTT ACT CAG AAT GAC TTT	1843
	His Phe Pro Ser Ser Leu Ala Phe Leu Asn Leu Thr Gln Asn Asp Phe	
	545 550 555	
50	GCT TGT ACT TGT GAA CAC CAG AGT TTC CTG CAA TGG ATC ARG SAC CAG	1891
	Ala Cys Thr Cys Glu His Gln Ser Phe Leu Gln Trp Ile Lys Asp Gln	
	560 565 570	
55	AGG CAG CTC TTG GTG GAA GTT GAA CGA ATG GAA TGT GCA ACA CCT TCA	1939
	Arg Gln Leu Leu Val Glu Val Glu Arg Met Glu Cys Ala Thr Pro Ser	
	575 580 585	

5	GAT AAG CAG GGC ATG CCT GTG CTG AGT TTG AAT ATC ACC TGT CAG ATG	1987
	Asp Lys Gln Gly Met Pro Val Leu Ser Leu Asn Ile Thr Cys Gln Met	
	590 595 600 605	
10	AAT AAG ACC ATC ATT GGT GTG TCG GTC CTC AGT GTG CTT GTA GTA TCT	2035
	Asn Lys Thr Ile Ile Gly Val Ser Val Leu Ser Val Leu Val Val Ser	
	610 615 620	
15	GTT GTA GCA GTT CTG GTC TAT AAG TTC TAT TTT CAC CTG ATG CTT CTT	2083
	Val Val Ala Val Leu Val Tyr Lys Phe Tyr Phe His Leu Met Leu Leu	
	625 630 635	
20	GCT GGC TGC ATA AAG TAT GGT AGA GGT GAA AAC ATC TAT GAT GCC TTT	2131
	Ala Gly Cys Ile Lys Tyr Gly Arg Gly Glu Asn Ile Tyr Asp Ala Phe	
	640 645 650	
25	GTT ATC TAC TCA AGC CAG GAT GAG GAC TGG GTA AGG AAT GAG CTA GTA	2179
	Val Ile Tyr Ser Ser Gln Asp Glu Asp Trp Val Arg Asn Glu Leu Val	
	655 660 665	
30	AAG AAT TTA GAA GAA GGG GTG CCT CCA TTT CAG CTC TGC CTT CAC TAC	2227
	Lys Asn Leu Glu Glu Gly Val Pro Pro Phe Gln Leu Cys Leu His Tyr	
	670 675 680	
35	AGA GAC TTT ATT CCC GGT GTG GCC AIT GCT GCC AAC ATC ATC CAT GAA	2275
	Arg Asp Phe Ile Pro Gly Val Ala Ile Ala Ala Asn Ile Ile His Glu	
	690 695 700	
40	GGT TTC CAT AAA AGC CGA AAG GTG ATT GTT GTG GTG TCC CAG CAC TTC	2323
	Gly Phe His Lys Ser Arg Lys Val Ile Val Val Val Ser Gln His Phe	
	705 710 715	
45	ATC CAG AGC CGC TGG TGT ATC TTT GAA TAT GAG ATT GCT CAG ACC TGG	2371
	Ile Gln Ser Arg Trp Cys Ile Phe Glu Tyr Glu Ile Ala Gln Thr Trp	
	720 725 730	
50	CAG TTT CTG AGC AGT CGT GCT GGT ATC ATC TTC ATT GTC CTG CAG AAG	2419
	Gln Phe Leu Ser Ser Arg Ala Gly Ile Ile Phe Ile Val Leu Gln Lys	
	735 740 745	
55	GTG GAG AAG ACC CTG CTC AGG CAG CAG GTG GAG CTG TAC CGC CTT CTC	2467
	Val Glu Lys Thr Leu Leu Arg Gln Gln Val Glu Leu Tyr Arg Leu Leu	
	750 755 760 765	
60	AGC AGG AAC ACT TAC CTG GAG TGG GAG GAC AGT GTC CTG GGG CGG CAC	2515
	Ser Arg Asn Thr Tyr Leu Glu Trp Glu Asp Ser Val Leu Gly Arg His	
	770 775 780	
65	ATC TTC TGG AGA CGA CTC AGA AAA GCC CTG CTG GAT GGT AAA TCA TGG	2563
	Ile Phe Trp Arg Arg Leu Arg Lys Ala Leu Leu Asp Gly Lys Ser Trp	
	785 790 795	

	AAT CCA GAA GGA ACA GTG GGT ACA GGA TGC AAT TGG CAG GAA GCA ACA	2611
	Asn Pro Glu Gly Thr Val Gly Thr Gly Cys Asn Trp Glu Glu Ala Thr	
	800 805 810	
5	TCT ATC TGAAGAGGAA AAATAAAAC CTCCTGAGGC ATTTCTTGCC CAGCTGGGTC	2667
	Ser Ile	
	815	
10	CAACACTTGT TCASTTAATA AGTATTAAAT GCTGCCACAT GTCAGGCCTT ATGCTAAGGG	2727
	TGAGTAATTC CATGGTGCAC TAGATATGCA GGGCTGCTAA TCTCAAGGAG CTTCCAGTGC	2787
	AGAGGGAATA AATGCTAGAC TAAAATACAG AGTCTTCCAG GTGGGCATTT CAACCAACTC	2847
15	AGTCAAGGAA CCCATGACAA AGAAGTCAT TTCAACTCTT ACCTCATCAA GTTGAATAAA	2907
	GACAGAGAAA ACAGAAAGAG ACATTGTCTT TTCTCTGAGT CTTTGAATG GAAATTGTAT	2967
	TATGTTATAG CCATCATAAA ACCATTTTGG TAGTTTTGAC TGAAGTGGGT GTTCACTTTT	3027
20	TCCTTTTGA TTGAATACAA TTAAATTCT ACTTGATGAC TGCAGTCGTC AAGGGGCTCC	3087
	TGATGCAAGA TGCCCTTCC ATTTTAAGTC TGTCTCTTA CAGAGTTAA AGTCTAATGG	3147
25	CTAATTCCTA AGGAAACCTG ATTAACACAT GTCACAAAC ATCCTGGTCA TTCTCGAACA	3207
	TGTTCTATTT TTAACTAAT CACCCCTGAT ATATTTTAT TTTTATATAT CCAGTTTCA	3267
	TTTTTTTACC TCTTGCCTAT AAGCTAATAT CATAAATAAG GTTGTCTAAG ACGTGCCTCA	3327
30	AATATCCATA TTAACCACTA TTTTCAAGG AAGTATGGAA AAGTACACTC TGTCACTTTC	3387
	TCACTCGATG TCATTCCAAA GTTATTGCCT ACTAAGTAAT GACTGTCATG AAAGCAGCAT	3447
35	TGAAATAATT TGTTTAAAGG GGGCACTCTT TTAAACGGGA AGAAATTTT CGCTTCCTGG	3507
	TCTTATCATG GACAATTTGG GCTAGAGCCA GGAAGGAAGT GGGATGACCT CAGGAAGTCA	3567
	CCTTTTCTTG ATTCCAGAAA CATATGGGCT GATAAACCCG GGGTGACCTC ATGAATGAG	3627
40	TTGCAGCAGA AGTTTATTTT TTTCAGAACA AGTGATGTTT GATGGACCTC TGAATCTCTT	3687
	TAGGGAGACA CAGATGGCTG GGATCCCTCC CCTGTACCTT TCTCACTGCC AGGAGAATA	3747
45	CGTGTGAAGG TATTCAACGC AGGGAGTATA CATTGCTGTT TCCTGTTGGG CAATGCTCCT	3807
	TGACCACATT TTGGGAAGAG TGGATGTTAT CATGAGAAA ACAATGTGTC TGGAATTAAT	3867
	GGGTTCTTA TAAAGAAGGT TCCCAGAAAA GAATGTTTAT TCCAGCTTCT TCAGGAAACA	3927
50	GGAACATTCA AGGAAAAGGA CAATCAGGAT GTCATCAGGG AAATGAAAAT AAAAACCACA	3987
	ATGAGATATC ACCTTATACC AGGTAGATGG CTACTATAAA AAAATGAAGT GTCATCAAGG	4047
55	ATATAGAGAA ATTGGAACCC TTCTTCACTG CTGGAGGGAA TGGAAAATGG TGTAGCCGT	4107

ATCAAAPACA GTACGGAGGT TTCTCAAAA TTAAAAATAG AACTGCTATA TGATCCAGCA 4167
 5 ATCTCACTTC TGTATATATA CCCAAAATAA TTGAAATCAG AATTTCAAGA AAATATTTAC 4227
 ACTCCCATGT TCATTGTGGC ACTCTTCACA ATCAGTGTTC CCAAAGTTAT GGAAACAACC 4287
 CAAATTECCA TTGGAAATA AATGGACAAA GGAAATGTGC ATATAACGTA CAATGGGGAT 4347
 10 ATTATTCAGC CTAAAAAAG GGGGGATCCT GTTATTTATG ACAACATGAA TAAACCCGGA 4407
 GGCCATTATG CTATGTAAA IGAGCAAGTA ACAGAAAGAC AAATACTGCC TGATTTTATT 4467
 15 TATATGAGGT TCTAAATAG TCAAATCAT AGAAGCAGAG AATAGAACAG TGTTCTCTAG 4527
 GGAAAAGGAG GAAGGGAGAA ATGAGGAAAT AGGGAGTTGT CTAATTGGTA TAAATTTATA 4587
 GTATGCAAGA TGAATTAGCT CTAAAGATCA GCTGTATAGC AGAGTTCGTA TAATGAACAA 4647
 20 TACTGTATTA TGCACTTAAC ATTTTGTAA GAGGGTACCT CTCATGTTAA GTGTTCTTAC 4707
 CATATACATA TACACAAGGA AGCTTTTGA GGTGATGGAT ATATTATTA CTTGATTGT 4767
 25 GGTGATGGTT TGACAGGTAT GTGACTATGT CTAACTCAT CAAATTGTAT ACATTAATA 4827
 TATGCAGTTT TATAATATCA AAAAAAAAAA AAAAAAA 4865
 MSASRLAGTLIPAMAFSLCVRPESWEPCVEVPNITYQCHELNFYKIPDNLPESTKNLDJSFNPLRHLGSYSEFSF
 30 PELQVLDLSRCEIQTIEDGAYQSLSHLSTLILTGNIQSLALGAFSGLSSLQKLVAVFTNLASLENFPIGHLKTL
 KELNVAHNLIQSEKLPYFSNLTNLEHLDLSSNKIQSIYCTDLRVLHQMPLNLSLDLSLNPMMFIQPGAFKEIR
 LHKLTLRNNEDSLNVMKTCIQGLAGLEVHRLVLGEFRNEGNLEKFKSALEGLCNLTIEEFRLAYLDYLDIID
 LFNCLTNVSSFSLSVSTIERVKDFSYNFGWQHLELVNCKEFGQFPTLKLKSLKRLTFTSNKGGNAFSEVDLPSLEF
 LDLSRNGISFKGCCSQSDFGTTSLKYLDLSFNGVITMSSNFLGLEQLEHLDFQHSNLKQMSFESVFLSLRNLIYL
 35 DISHTHTRVAFNGIFNGLSSLEVLMAGNSFQENFLPDI FTELRLTFDLSQCQLEQLSPTAFNSLSLQVLNM
 SHNNEFSLDTPPYKCLNSLQVLDYSLNHIMTSKKQELQHFPSLAFLNLTQNDFACTCEHQSFLQWIKDQRQLLV
 EVERMECATPSDKQGMPLVSLNITCQMNKTIIGVSVLSVLVSVVAVLVYKFYFHLMLLAGCICKYGRGENIYDAF
 VIYSSQEDDWVRNELVKNLEEGVPPFQLCLHYRDFIPGVAIAANIIEGFHKSRRKIVVVVSHFIQSRWCIFEYE
 IAQTWQFLSSRAGIIFIVLQKVEKTLRQQVELYRLSRNTYLEWEDSVLGRHIFWRRLRKALLDGKSWNPEGT
 GTGCNWQEATSI

Table 5: Partial nucleotide and amino acid sequences (see SEQ ID NO: 9 and 10) of a mammalian, e.g., primate, human, DNAX Tc11 like Receptor 3 (DRLR5).

5	TGT TGG GAT GTT TTT GAG GGA CTT TCT CAT CTT CAA GTT CTG TAT TTG	48
	Cys Trp Asp Val Phe Glu Gly Leu Ser His Leu Gln Val Leu Tyr Leu	
	1 5 10 15	
10	AAT CAT AAC TAT CTT AAT TCC CTT CCA CCA GGA GTA TTT AGC CAT CTG	96
	Asn His Asn Tyr Leu Asn Ser Leu Pro Pro Gly Val Phe Ser His Leu	
	20 25 30	
15	ACT GCA TTA AGG GGA CTA AGC CTC AAC TCC AAC AGG CTG ACA GTT CTT	144
	Thr Ala Leu Arg Gly Leu Ser Leu Asn Ser Asn Arg Leu Thr Val Leu	
	35 40 45	
20	TCT CAC AAT GAT TTA CCT GCT AAT TTA GAG ATC CTG GAC ATA TCC AGG	192
	Ser His Asn Asp Leu Pro Ala Asn Leu Glu Ile Leu Asp Ile Ser Arg	
	50 55 60	
25	AAC CAG CTC CTA GCT CCT AAT CCT GAT GTA TTT GTA TCA CTT AGT GTC	240
	Asn Gln Leu Leu Ala Pro Asn Pro Asp Val Phe Val Ser Leu Ser Val	
	65 70 75 80	
30	TTG GAT ATA ACT CAT AAC AAG TTC ATT TGT GAA TGT GAA CTT AGC ACT	288
	Leu Asp Ile Thr His Asn Lys Phe Ile Cys Glu Cys Glu Leu Ser Thr	
	85 90 95	
35	TTT ATC AAT TGG CTC AAT CAC ACC AAT GTC ACT ATA GCT GGG CCT CCT	336
	Phe Ile Asn Trp Leu Asn His Thr Asn Val Thr Ile Ala Gly Pro Pro	
	100 105 110	
40	GCA GAC ATA TAT TGT GTG TAC CCT GAC TCG TTC TCT GGG GTT TCC CTC	384
	Ala Asp Ile Tyr Cys Val Tyr Pro Asp Ser Phe Ser Gly Val Ser Leu	
	115 120 125	
45	TTC TCT CTT TCC ACG GAA GGT TGT GAT GAA GAG GAA GTC TTA AAG TCC	432
	Phe Ser Leu Ser Thr Glu Gly Cys Asp Glu Glu Val Leu Lys Ser	
	130 135 140	
50	CTA AAG TTC TCC CTT TTC ATT GTA TGC ACT GTC ACT CTG ACT CTG TTC	480
	Leu Lys Phe Ser Leu Phe Ile Val Cys Thr Val Thr Leu Thr Leu Phe	
	145 150 155 160	
55	CTC ATG ACC ATC CTC ACA GTC ACA AAG TTC CGG GGC TTC TGT TTT ATC	528
	Leu Met Thr Ile Leu Thr Val Thr Lys Phe Arg Gly Phe Cys Phe Ile	
	165 170 175	
60	TGT TAT AAG ACA GCC CAG AGA CTS GTS TTC AAG GAC CAT CCC CAG GGC	576
	Cys Tyr Lys Thr Ala Gln Arg Leu Val Phe Lys Asp His Pro Gln Gly	
	180 185 190	
65	ACA GAA CCT GAT ATG TAC AAA TAT GAT GCC TAT TTG TGC TTC AGC AGC	624
	Thr Glu Pro Asp Met Tyr Lys Tyr Asp Ala Tyr Leu Cys Phe Ser Ser	
	195 200 205	

AAA GAC TTC ACA TGG GTG CAG AAT GCT TTG CTC AAA CAC CTG GAC ACT 672
 Lys Asp Phe Thr Trp Val Gln Asn Ala Leu Leu Lys His Leu Asp Thr
 210 215 220

5 CAA TAC AGT GAC CAA AAC AGA TTC AAC CTG TGC TTT GAA GAA AGA GAC 720
 Gln Tyr Ser Asp Gln Asn Arg Phe Asn Leu Cys Phe Glu Glu Arg Asp
 225 230 235 240

10 TTT GTC CCA GGA GAA AAC CGC ATT GCC AAT ATC CAG GAT GCC ATC TGG 763
 Phe Val Pro Gly Glu Asn Arg Ile Ala Asn Ile Gln Asp Ala Ile Trp
 245 250 255

15 AAC AGT AGA AAG ATC GTT TGT CTT GTG AGC AGA CAC TTC CTT AGA GAT 816
 Asn Ser Arg Lys Ile Val Cys Leu Val Ser Arg His Phe Leu Arg Asp
 260 265 270

20 GGC TGG TGC CTT GAA GCC TTC AGT TAT GCC CAG GGC AGG TGC TTA TCT 864
 Gly Trp Cys Leu Glu Ala Phe Ser Tyr Ala Gln Gly Arg Cys Leu Ser
 275 280 285

25 GAC CTT AAC AGT GCT CTC ATC ATG GTG GTG GTT GGG TCC TTG TCC CAG 912
 Asp Leu Asn Ser Ala Leu Ile Met Val Val Val Gly Ser Leu Ser Gln
 290 295 300

TAC CAG TTG ATG AAA CAT CAA TCC ATC AGA GGC TTT GTA CAG AAA CAG 960
 Tyr Gln Leu Met Lys His Gln Ser Ile Arg Gly Phe Val Gln Lys Gln
 305 310 315 320

30 CAG TAT TTG AGG TGG CCT GAG GAT CTC CAG GAT GTT GGC TGG TTT CTT 1008
 Gln Tyr Leu Arg Trp Pro Glu Asp Leu Gln Asp Val Gly Trp Phe Leu
 325 330 335

35 CAT AAA CTC TCT CAA CAG ATA CTA AAG AAA GAA AAG GAA AAG AAG AAA 1056
 His Lys Leu Ser Gln Gln Ile Leu Lys Lys Glu Lys Glu Lys Lys Lys
 340 345 350

40 GAC AAT AAC ATT CCG TTG CAA ACT GTA GCA ACC ATC TCC TAATCAAAGG 1105
 Asp Asn Asn Ile Pro Leu Gln Thr Val Ala Thr Ile Ser
 355 360 365

45 AGCAATTTCC AACTTATCTC AAGCCACAAA TAACCTCTCA CTTGTATTT GCACCAAGTT 1165
 ATCATTTTGG GGTCTCTCTT GGAGGTTTTT TTTTCTTTT TGCTACTATG AAAACAACAT 1225
 AAATCTCTCA ATTTTCGTAT CAAAAA AAAA AAAA TGGCGGCCGC 1275

50 CWDVFEGLSHLQVLYLNHNYLNSLPPGVFSLHTALRGLSLNSNRLTVLSHNDLPANLEILDISRNOQLLAPNPVDF
 VLSVLDITHNKFCECELSTFINWLNHTNVTIAGPPADIYCVYPDSTFSGVSLFSLSTEGCDEEEVLKSLKFSLF
 IVCTVTLTFLMTLELVKFRGFCFICYKTAQRLVFKDHPQGTEPDYKYDAYLCFSSKDFTWVQNALLKHLDTQ
 YSDQNRNLCFFERDFVPGENRIANIQDAIWNRSRKIVCLVSRHFLRDGWCLEAFSYAQGRCLSDLNSALIMVVVG
 SLSQYQLMKHQSIKRGFVQKQYLRWPEELQJVGWFLHKLSSQILKKEKEKKDNNIPLQTVATIS

Table 6: Nucleotide and amino acid sequences of mammalian, e.g., primate or rodent DNAX Toll like Receptor 6 (DTRLR6). SEQ ID NO: 11 and 12 are from primate, e.g., human; SEQ ID NO: 13 and 14 are from rodent, e.g., mouse.

5	primate:		
	ATG TGG ACA CTG AAG AGA CTA ATT CTT ATC CTT TTT AAC ATA ATC CTA	48	
	Met Trp Thr Leu Lys Arg Leu Ile Leu Ile Leu Phe Asn Ile Ile Leu		
	-22 -20 -15 -10		
10	ATT TCC AAA CTC CTT GGG GCT AGA TGG TTT CCT AAA ACT CTG CCC TGT	96	
	Ile Ser Lys Leu Leu Gly Ala Arg Trp Phe Pro Lys Thr Leu Pro Cys		
	-5 1 5 10		
15	GAT GTC ACT CTG GAT GTT CCA AAG AAC CAT GTG ATC GTG GAC TGC ACA	144	
	Asp Val Thr Leu Asp Val Pro Lys Asn His Val Ile Val Asp Cys Thr		
	15 20 25		
20	GAC AAG CAT TTG ACA GAA ATT CCT GGA GGT ATT CCC ACG AAC ACC ACG	192	
	Asp Lys His Leu Thr Glu Ile Pro Gly Gly Ile Pro Thr Asn Thr Thr		
	30 35 40		
25	AAC CTC ACC CTC ACC ATT AAC CAC ATA CCA GAC ATC TCC CCA GCG TCC	240	
	Asn Leu Thr Leu Thr Ile Asn His Ile Pro Asp Ile Ser Pro Ala Ser		
	45 50 55		
30	TTT CAC AGA CTC GAC CAT CTG GTA GAG ATC GAT TTC AGA TGC AAC TGT	288	
	Phe His Arg Leu Asp His Leu Val Glu Ile Asp Phe Arg Cys Asn Cys		
	60 65 70		
35	GTA CCT ATT CCA CTG GGG TCA AAA AAC AAC ATG TGC ATC AAG AGG CTG	336	
	Val Pro Ile Pro Leu Gly Ser Lys Asn Asn Met Cys Ile Lys Arg Leu		
	75 80 85 90		
40	CAG ATT AAA CCC AGA AGC TTT AGT GGA CTC ACT TAT TTA AAA TCC CTT	384	
	Gln Ile Lys Pro Arg Ser Phe Ser Gly Leu Thr Tyr Leu Lys Ser Leu		
	95 100 105		
45	TAC CTG GAT CGA AAC CAG CTA CTA GAG ATA CCG CAG GGC CTC CCG CCT	432	
	Tyr Leu Asp Gly Asn Gln Leu Leu Glu Ile Pro Gln Gly Leu Pro Pro		
	110 115 120		
50	AGC TTA CAG CTT CTC AGC CTT GAG GCC AAC AAC ATC TTT TCC ATC AGA	480	
	Ser Leu Gln Leu Leu Ser Leu Glu Ala Asn Asn Ile Phe Ser Ile Arg		
	125 130 135		
55	AAA GAG AAT CTA ACA GAA CTG GCC AAC ATA GAA ATA CTC TAC CTG GGC	528	
	Lys Glu Asn Leu Thr Glu Leu Ala Asn Ile Glu Ile Leu Tyr Leu Gly		
	140 145 150		
60	CAA AAC TGT TAT TAT CGA AAT CCT TGT TAT GTT TCA TAT TCA ATA GAG	576	
	Gln Asn Cys Tyr Tyr Arg Asn Pro Cys Tyr Val Ser Tyr Ser Ile Glu		
	155 160 165 170		

	AAA GAT GCC TTC CTA AAC TTG ACA AAG TTA AAA GTG CTC TCC CTG AAA	624
	Lys Asp Ala Phe Leu Asn Leu Thr Lys Leu Lys Val Leu Ser Leu Lys	
	175 180 185	
5	GAT AAC AAT GTC ACA GCC GTC CCT ACT GTT TTG CCA TCT ACT TTA ACA	672
	Asp Asn Asn Val Thr Ala Val Pro Thr Val Leu Pro Ser Thr Leu Thr	
	190 195 200	
10	GAA CTA TAT CTC TAC AAC AAC ATG ATT GCA AAA ATC CAA GAA GAT GAT	720
	Glu Leu Tyr Leu Tyr Asn Asn Met Ile Ala Lys Ile Gln Glu Asp Asp	
	205 210 215	
15	TTT AAT AAC CTC AAC CAA TTA CAA ATT CTT GAC CTA AGT GGA AAT TGC	768
	Phe Asn Asn Leu Asn Gln Leu Gln Ile Leu Asp Leu Ser Gly Asn Cys	
	220 225 230	
20	CCT CGT TGT TAT AAT GCC CCA TTT CCT TGT GCG CCG TGT AAA AAT AAT	816
	Pro Arg Cys Tyr Asn Ala Pro Phe Pro Cys Ala Pro Cys Lys Asn Asn	
	235 240 245 250	
25	TCT CCC CTA CAG ATC CCT GTA AAT GCT TTT GAT GCG CTG ACA GAA TTA	864
	Ser Pro Leu Gln Ile Pro Val Asn Ala Phe Asp Ala Leu Thr Glu Leu	
	255 260 265	
30	AAA GTT TTA CGT CTA CAC AGT AAC TCT CTT CAG CAT GTG CCC CCA AGA	912
	Lys Val Leu Arg Leu His Ser Asn Ser Leu Gln His Val Pro Pro Arg	
	270 275 280	
35	TGG TTT AAG AAC ATC AAC AAA CTC CAG GAA CTG GAT CTG TCC CAA AAC	960
	Trp Phe Lys Asn Ile Asn Lys Leu Gln Glu Leu Asp Leu Ser Gln Asn	
	285 290 295	
40	TTC TTG GCC AAA GAA ATT GGG GAT GCT AAA TTT CTG CAT TTT CTC CCC	1008
	Phe Leu Ala Lys Glu Ile Gly Asp Ala Lys Phe Leu His Phe Leu Pro	
	300 305 310	
45	AGC CTC ATC CAA TTG GAT CTG TCT TTC AAT TTT GAA CTT CAC GTC TAT	1056
	Ser Leu Ile Gln Leu Asp Leu Ser Phe Asn Phe Glu Leu Gln Val Tyr	
	315 320 325 330	
50	CGT GCA TCT ATG AAT CTA TCA CAA GCA TTT TCT TCA CTG AAA AGC CTG	1104
	Arg Ala Ser Met Asn Leu Ser Gln Ala Phe Ser Ser Leu Lys Ser Leu	
	335 340 345	
55	AAA ATT CTG CGG ATC AGA GGA TAT GTC TTT AAA GAG ITG AAA AGC TTT	1152
	Lys Ile Leu Arg Ile Arg Gly Tyr Val Phe Lys Glu Leu Lys Ser Phe	
	350 355 360	
60	AAC CTC TCG CCA TTA CAT AAT CTT CAA AAT CTT GAA CTT CTT GAT CTT	1200
	Asn Leu Ser Pro Leu His Asn Leu Gln Asn Leu Glu Val Leu Asp Leu	
	365 370 375	
65	GGC ACT AAC TTT ATA AAA ATT GCT AAC CTC AGC ATG TTT AAA CAA TTT	1248
	Gly Thr Asn Phe Ile Lys Ile Ala Asn Leu Ser Met Phe Lys Gln Phe	
	380 385 390	

5	AAA AGA CTG AAA GTC ATA GAT CTT TCA GTG AAT AAA ATA TCA CCT TCA Lys Arg Leu Lys Val Ile Asp Leu Ser Val Asn Lys Ile Ser Pro Ser 395 400 405 410	1296
	GGA GAT TCA AGT GAA GTT GGC TTC TGC TCA AAT GCC AGA ACT TCT GTA Gly Asp Ser Ser Glu Val Gly Phe Cys Ser Asn Ala Arg Thr Ser Val 415 420 425	1344
10	GAA AGT TAT GAA CCC CAG GTC CTG GAA CAA TTA CAT TAT TTC AGA TAT Glu Ser Tyr Glu Pro Gln Val Leu Glu Gln Leu His Tyr Phe Arg Tyr 430 435 440	1392
15	GAT AAG TAT GCA AGG AGT TGC AGA TTC AAA AAC AAA GAG GCT TCT TTC Asp Lys Tyr Ala Arg Ser Cys Arg Phe Lys Asn Lys Glu Ala Ser Phe 445 450 455	1440
20	ATG TCT GTT AAT GAA AGC TGC TAC AAG TAT GGG CAG ACC TTG GAT CTA Met Ser Val Asn Glu Ser Cys Tyr Lys Tyr Gly Gln Thr Leu Asp Leu 460 465 470	1488
25	AGT AAA AAT AGT ATA TTT TTT GTC AAG TCC TCT GAT TTT CAG CAT CTT Ser Lys Asn Ser Ile Phe Phe Val Lys Ser Ser Asp Phe Gln His Leu 475 480 485 490	1536
	TCT TTC CTC AAA TGC CTG AAT CTG TCA GGA AAT CTC ATT AGC CAA ACT Ser Phe Leu Lys Cys Leu Asn Leu Ser Gly Asn Leu Ile Ser Gln Thr 495 500 505	1584
30	CTT AAT GGC AGT GAA TTC CAA CCT TTA GCA GAG CTG AGA TAT TTG GAC Leu Asn Gly Ser Glu Phe Gln Pro Leu Ala Glu Leu Arg Tyr Leu Asp 510 515 520	1632
35	TTC TCC AAC AAC CGG CTT GAT TTA CTC CAT TCA ACA GCA TTT GAA GAG Phe Ser Asn Asn Arg Leu Asp Leu Leu His Ser Thr Ala Phe Glu Glu 525 530 535	1680
40	CTT CAC AAA CTG GAA GTT CTG GAT ATA AGC AGT AAT AGC CAT TAT TTT Leu His Lys Leu Glu Val Leu Asp Ile Ser Ser Asn Ser His Tyr Phe 540 545 550	1728
45	CAA TCA GAA GGA ATT ACT CAT ATG CTA AAC TTT ACC AAG AAC CTA AAG Gln Ser Glu Gly Ile Thr His Met Leu Asn Phe Thr Lys Asn Leu Lys 555 560 565 570	1776
	GTT CTG CAG AAA CTG ATG ATG AAC GAC AAT GAC ATC TCT TCC TCC ACC Val Leu Gln Lys Leu Met Met Asn Asp Asn Asp Ile Ser Ser Ser Thr 575 580 585	1824
50	AGC AGG ACC ATG GAG AGT GAG TCT CTT AGA ACT CTG GAA TTC AGA GGA Ser Arg Thr Met Glu Ser Glu Ser Leu Arg Thr Leu Glu Phe Arg Gly 590 595 600	1872

	AAT CAC TTA GAT GTT TTA TGG AGA GAA GGT GAT AAC AGA TAC TTA CAA Asn His Leu Asp Val Leu Trp Arg Glu Gly Asp Asn Arg Tyr Leu Gln 605 610 615	1920
5	TTA TTC AAG AAT CTG CTA AAA TTA GAG GAA TTA GAC ATC TCT AAA AAT Leu Phe Lys Asn Leu Leu Lys Leu Glu Glu Leu Asp Ile Ser Lys Asn 620 625 630	1968
10	TCC CTA AGT TTC TTG CCT TCT GGA GTT TTT GAT GGT ATG CCT CCA AAT Ser Leu Ser Phe Leu Pro Ser Gly Val Phe Asp Gly Met Pro Pro Asn 635 640 645 650	2016
15	CTA AAG AAT CTC TCT TTG GCC AAA AAT GGG CTC AAA TCT TTC AGT TGG Leu Lys Asn Leu Ser Leu Ala Lys Asn Gly Leu Lys Ser Phe Ser Trp 655 660 665	2064
20	AAG AAA CTC CAG TGT CTA AAG AAC CTG GAA ACT TTG GAC CTC AGC CAC Lys Lys Leu Gln Cys Leu Lys Asn Leu Glu Thr Leu Asp Leu Ser His 670 675 680	2112
	AAC CAA CTG ACC ACT GTC CCT GAG AGA TTA TCC AAC TGT TCC AGA AGC Asn Gln Leu Thr Thr Val Pro Glu Arg Leu Ser Asn Cys Ser Arg Ser 685 690 695	2160
25	CTC AAG AAT CTG ATT CTT AAG AAT AAT CAA ATC AGG AGT CTG ACG AAG Leu Lys Asn Leu Ile Leu Lys Asn Asn Gln Ile Arg Ser Leu Thr Lys 700 705 710	2208
30	TAT TTT CTA CAA GAT GCC TTC CAG TTG CGA TAT CTG GAT CTC AGC TCA Tyr Phe Leu Gln Asp Ala Phe Gln Leu Arg Tyr Leu Asp Leu Ser Ser 715 720 725 730	2256
35	AAT AAA ATC CAG ATG ATC CAA AAG ACC AGC TTC CCA GAA AAT GTC CTC Asn Lys Ile Gln Met Ile Gln Lys Thr Ser Phe Pro Glu Asn Val Leu 735 740 745	2304
40	AAC AAT CTG AAG ATG TTG CTT TTG CAT CAT AAT CGG TTT CTG TGC ACC Asn Asn Leu Lys Met Leu Leu Leu His His Asn Arg Phe Leu Cys Thr 750 755 760	2352
	TGT GAT GCT GTG TGG TTT GTC TGG TGG GTT AAC CAT ACG GAG GTG ACT Cys Asp Ala Val Trp Phe Val Trp Trp Val Asn His Thr Glu Val Thr 765 770 775	2400
45	ATT CCT TAC CTG GCC ACA GAT GTG ACT TGT GTG GGG CCA GGA GCA CAC Ile Pro Tyr Leu Ala Thr Asp Val Thr Cys Val Gly Pro Gly Ala His 780 785 790	2448
50	AAG GGC CAA AGT GTG ATC TCC CTG GAT CTG TAC ACC TGT GAG TTA GAT Lys Gly Gln Ser Val Ile Ser Leu Asp Leu Tyr Thr Cys Glu Leu Asp 795 800 805 810	2496
55	CTG ACT AAC CTG ATT CTG TTC TCA CTT TCC ATA TCT GTA TCT CTC TTT Leu Thr Asn Leu Ile Leu Phe Ser Leu Ser Ile Ser Val Ser Leu Phe 815 820 825	2544

	CTC ATG GTG ATG ATG ACA GCA AGT CAC CTC TAC TTC TGG GAT GTG TGG	2592
	Leu Met Val Met Met Thr Ala Ser His Leu Tyr Phe Trp Asp Val Trp	
	830 835 840	
5	TAT ATT TAC CAT TTC TGT AAG GCC AAG ATA AAG GGG TAT CAG CGT CTA	2640
	Tyr Ile Tyr His Phe Cys Lys Ala Lys Ile Lys Gly Tyr Gln Arg Leu	
	845 850 855	
10	ATA TCA CCA GAC TGT TGC TAT GAT GCT TTT ATT GTG TAT GAC ACT AAA	2689
	Ile Ser Pro Asp Cys Cys Tyr Asp Ala Phe Ile Val Tyr Asp Thr Lys	
	860 855 870	
15	GAC CCA GCT GTG ACC GAG TGG GTT TTG GCT GAG CTG GTG GCC AAA CTG	2736
	Asp Pro Ala Val Thr Glu Trp Val Leu Ala Glu Leu Val Ala Lys Leu	
	875 880 895 890	
20	GAA GAC CCA AGA GAG AAA CAT TTT AAT TTA TGT CTC GAG GAA AGG GAC	2784
	Glu Asp Pro Arg Glu Lys His Phe Asn Leu Cys Leu Glu Glu Arg Asp	
	895 900 905	
25	TGG TTA CCA GGG CAG CCA GTT CTG GAA AAC CTT TCC CAG AGC ATA CAG	2832
	Trp Leu Pro Gly Gln Pro Val Leu Glu Asn Leu Ser Gln Ser Ile Gln	
	910 915 920	
30	CTT AGC AAA AAG ACA GTG TTT GTG ATG ACA GAC AAG TAT GCA AAG ACT	2880
	Leu Ser Lys Lys Thr Val Phe Val Met Thr Asp Lys Tyr Ala Lys Thr	
	925 930 935	
35	GAA AAT TTT AAG ATA GCA TTT TAC TTG TCC CAT CAG AGG CTC ATG GAT	2928
	Glu Asn Phe Lys Ile Ala Phe Tyr Leu Ser His Gln Arg Leu Met Asp	
	940 945 950	
40	GAA AAA GTT GAT GTG ATT ATC TTG ACA TTT CTT GAG AAG CCC TTT CAG	2976
	Glu Lys Val Asp Val Ile Ile Leu Ile Phe Leu Glu Lys Pro Phe Gln	
	955 960 965 970	
45	AAG TCC AAG TTC CTC CAG CTC CGG AAA AGG CTC TGT GGG AGT TCT GTC	3024
	Lys Ser Lys Phe Leu Gln Leu Arg Lys Arg Leu Cys Gly Ser Ser Val	
	975 980 985	
50	CTT GAG TGG CCA ACA AAC CCG CAA GCT CAC CCA TAC TTC TGG CAG TGT	3072
	Leu Glu Trp Pro Thr Asn Pro Gln Ala His Pro Tyr Phe Trp Gln Cys	
	990 995 1000	
55	CTA AAG AAC GCC CTG GCC ACA GAC AAT CAT GTG GCC TAT AGT CAG GTG	3120
	Leu Lys Asn Ala Leu Ala Thr Asp Asn His Val Ala Tyr Ser Gln Val	
	1005 1010 1015	
60	TTC AAG GAA ACG GTC TAG	3138
	Phe Lys Glu Thr Val	
	1020	
65	MWTLKRLILILFNILISKLLGARWFPKTLPCDVTLEVPKNHIVDCTDKHLTEIPGGIPTNTTNIILTLINHIP	
	DISPASFHRLDHLVEIDFRNCNCPVPIPLGSKNNMCIKRLQIKPRSFSGLYLKSLEYLOGNQLLEIPQGLPPSLQL	

LSLEANNIFSIRKENLTELANIEILYLQNCYIRNFCYVSYSIEKDAFLNLTCLKVLSLKDNNTAVPTVLPST
LTELYLYNNMIAKIQEDDFNNLNQLQILDLSGNCPRCYNAPFPCAPCKNNSPLQIPVNAFDALTELKVLRLHSN
SLQHVPPRWFKNINKLQELDLSQNFLAKEIGDAKFLHFLPSLIQLDLSFNFEHQVYRASMNLSQAFSSLKSLKI
LRIRGYVFKELKSFNLSPLHNLQNLEVLGLGTNFIKIANLSMFKQFKRLKVIDLSVNKISPSGDSSEVGFCSNA
5 RTSVESYEPQVLEQLHYFRYDKYARSCRFKNKEASEMSVNESCYKYGQTEQLSKNSIFFVKSSDFQHLSTLKCL
NLGSGNLISQTLNGSEFQPLAELRYLOFSNNRLDLLHSTAFEELHKLEVLDTSSNSHYFQSEGITHMLNFTKNLK
VLQKLMNDNDISSSTSRTMESESLRTEFRGNHLDVLRWREGDNRYLQLFKNLKLEELDISKNSLSFLPSGVF
DGNP?NLKNLSLAKNGLKSFSWKKLQCLKNLETLDLSKNQLTTVPERLSNCSRSKKNLILKNNQIRSLTKYFLO
DAFQLRYLDLSSNKIQMIQKTSFPENVLNNLKMLLLHHNRFLCTCDVWVFWVWNHTEVTIPYLATDVTCVGP
10 AHKQSVISLDLYTCELDLTNLILFSLISVSLFLMVMMTASHLYFNDVWYIYHFCKAKIKGYQRLISPCCYD
AFIVYCTKDPAVTEWVLAEVLAKLEDPREKHFNLCLEERDWLPGQPVLENLSQSIQLSKKTVFVMTDKYAKTEN
FKIAFYLSHQRLMDEKVDVILIFLEKPFQKSKFLQLRKRLCGSSVLEWPTNPQAHFYFWQCLKNALATDNHVA
YSQVFKETV

rodent (SEQ ID NO: 13 and 14):

5	CTT GGA AAA CCT CTT CAG AAG TCT AAG TTT CTT CAG CTC AGG AAG AGA Leu Gly Lys Pro Leu Gln Lys Ser Lys Phe Leu Gln Leu Arg Lys Arg	48
	1 5 10 15	
10	CTC TGC AGG AGC TCT GTC CTT GAG TGG CCT GCA AAT CCA CAG GCT CAC Leu Cys Arg Ser Ser Val Leu Glu Trp Pro Ala Asn Pro Gln Ala His	96
	20 25 30	
15	CCA TAC TTC TGG CAG TGC CTG AAA AAT GCC CTG ACC ACA GAC AAT CAT Pro Tyr Phe Trp Gln Cys Leu Lys Asn Ala Leu Thr Thr Asp Asn His	144
	35 40 45	
20	GTG GCT TAT AGT CAA ATG TTC AAG GAA ACA GTC TAG Val Ala Tyr Ser Gln Met Phe Lys Glu Thr Val	180
	50 55	
	LGKPLQKSKFLQLRKRLCRSSVLEWPNANPQAHFYFWQCLKALTTDNHVAYSQMFKETV	
25	additional rodent, e.g., mouse sequences:	
	upstream (SEQ ID NO: 27 and 28); nucleotides 186, 196, 217, 276, and 300 designated C, each may be A, C, G, or T:	
30	TCC TAT TCT ATG GAA AAA GAT GCT TTC CTA TTT ATG AGA AAT TTG AAG Ser Tyr Ser Met Glu Lys Asp Ala Phe Leu Phe Met Arg Asn Leu Lys	48
	1 5 10 15	
35	GTT CTC TCA CTA AAA GAT AAC AAT GTC ACA GCT GTC CCC ACC ACT TTG Val Leu Ser Leu Lys Asp Asn Asn Val Thr Ala Val Pro Thr Thr Leu	96
	20 25 30	
40	CCA CCT AAT TTA CTA GAG CTC TAT CTT TAT AAC AAT ATC ATT AAG AAA Pro Pro Asn Leu Leu Glu Leu Tyr Leu Tyr Asn Asn Ile Ile Lys Lys	144
	35 40 45	
45	ATC CAA GAA AAT GAT TTC AAT AAC CTC AAT GAG TTG CAA GTC CTT GAC Ile Gln Glu Asn Asp Phe Asn Asn Leu Asn Glu Leu Gln Val Leu Asp	192
	50 55 60	
50	CTA CGT GGA AAT TGC CCT CGA TGT CAT AAT GTC CCA TAT CCG TGT ACA Leu Arg Gly Asn Cys Pro Arg Cys His Asn Val Pro Tyr Pro Cys Thr	240
	65 70 75 80	
	CCG TGT GAA AAT AAT TCC CCC TTA CAG ATC CAT GAC AAT GCT TTC AAT Pro Cys Glu Asn Asn Ser Pro Leu Gln Ile His Asp Asn Ala Phe Asn	288
	85 90 95	
	TCA TCG ACA GAC Ser Ser Thr Asp	300
	100	

SYSMEKDAFLFMRNLKVLSLKDNVNTAVPTTLPPNLLLELYLYNNIIKKIQENDFNNLNELQXLDLXGNCPRCXNV
 PYPCTPCENNSPLQIHKNAFNSSTX

5	downstream (SEQ ID NO: 29 and 30); nucleotide 1643 designated A, may be A or G; nucleotide 1664 designated C, may be A, C, G, or T; nucleotides 1690 and 1735 designated G, may be G or T; nucleotide 1719 designated C, may be C or T; and nucleotide 1727 designated A, may be A, G, or T:																		
10	TCT CCA GAA ATT CCC TGG AAT TCC TTG CCT CCT GAG GTT TTT GAG GGT	48																	
	Ser Pro Glu Ile Pro Trp Asn Ser Leu Pro Pro Glu Val Phe Glu Gly																		
	1 5 10 15																		
15	ATG CCG CCA AAT CTA AAG AAT CTC TCC TTG GCC AAA AAT GGG CTC AAA	96																	
	Met Pro Pro Asn Leu Lys Asn Leu Ser Leu Ala Lys Asn Gly Leu Lys																		
	20 25 30																		
20	TCT TTC TTT TGG GAC AGA CTC CAG TTA CTG AAG CAT TTG GAA ATT TTG	144																	
	Ser Phe Phe Trp Asp Arg Leu Gln Leu Leu Lys His Leu Glu Ile Leu																		
	35 40 45																		
25	GAC CTC AGC CAT AAC CAG CTG ACA AAA GTA CCT GAG AGA TTG GCC AAC	192																	
	Asp Leu Ser His Asn Gln Leu Thr Lys Val Pro Glu Arg Leu Ala Asn																		
	50 55 60																		
30	TGT TCC AAA AGT CTC ACA ACA CTG ATT CTT AAG CAT AAT CAA ATC AGG	240																	
	Cys Ser Lys Ser Leu Thr Thr Leu Ile Leu Lys His Asn Gln Ile Arg																		
	65 70 75 80																		
35	CAA TTG ACA AAA TAT TTT CTA GAA GAT GCT TCG CAA TTG CGC TAT CTA	288																	
	Gln Leu Thr Lys Tyr Phe Leu Glu Asp Ala Leu Gln Leu Arg Tyr Leu																		
	85 90 95																		
40	GAC ATC AGT TCA AAT AAA ATC CAG GTC ATT CAG AAG ACT AGC TTC CCA	336																	
	Asp Ile Ser Ser Asn Lys Ile Gln Val Ile Gln Lys Thr Ser Phe Pro																		
	100 105 110																		
45	GAA AAT GTC CTC AAC AAT CTG GAG ATG TTG GTT TTA CAT CAC AAT CGC	384																	
	Glu Asn Val Leu Asn Asn Leu Glu Met Leu Val Leu His His Asn Arg																		
	115 120 125																		
50	TTT CTT TGC AAC TGT GAT GCT GTG TGG TTT GTC TGG TGG GTT AAC CAT	432																	
	Phe Leu Cys Asn Cys Asp Ala Val Trp Phe Val Trp Trp Val Asn His																		
	130 135 140																		
55	ACA GAT GTC ACT ATT CCA TAC CTG GCC ACT GAT GTG ACT TGT GTA GGT	480																	
	Thr Asp Val Thr Ile Pro Tyr Leu Ala Thr Asp Val Thr Cys Val Gly																		
	145 150 155 160																		
60	CCA GGA GCA CAC AAA GGT CAA AGT GTC ATA TCC CTT GAT CTG TAT ACG	528																	
	Pro Gly Ala His Lys Gly Gln Ser Val Ile Ser Leu Asp Leu Tyr Thr																		
	165 170 175																		

	TGT GAG TTA GAT CTC ACA AAC CTG ATT CTG TTC TCA GTT TCC ATA TCA	576
	Cys Glu Leu Asp Leu Thr Asn Leu Ile Leu Phe Ser Val Ser Ile Ser	
	18C 185 190	
5	TCA GTC CTC TTT CTT ATG GTA GTT ATG ACA ACA AGT CAC CTC TTT TTC	624
	Ser Val Leu Phe Leu Met Val Val Met Thr Thr Ser His Leu Phe Phe	
	195 200 205	
10	TGG GAT ATG TGG TAC ATT TAT TAT TTT TGG AAA GCA AAG ATA AAG GGG	672
	Trp Asp Met Trp Tyr Ile Tyr Tyr Phe Trp Lys Ala Lys Ile Lys Gly	
	210 215 220	
15	TAT CCA GCA TCT GCA ATC CCA TGG AGT CCT TGT TAT GAT GCT TTT ATT	720
	Tyr Pro Ala Ser Ala Ile Pro Trp Ser Pro Cys Tyr Asp Ala Phe Ile	
	225 230 235 240	
20	GTG TAT GAC ACT AAA AAC TCA GCT GTG ACA GAA TGG GTT TTG CAG GAG	768
	Val Tyr Asp Thr Lys Asn Ser Ala Val Thr Glu Trp Val Leu Gln Glu	
	245 250 255	
	CTG GTG GCA AAA TTG GAA GAT CCA AGA GAA AAA CAC TTC AAT TTG TGT	816
	Leu Val Ala Lys Leu Glu Asp Pro Arg Glu Lys His Phe Asn Leu Cys	
	260 265 270	
25	CTA GAA GAA AGA GAC TGG CTA CCA GGA CAG CCA GTT CTA GAA AAC CTT	864
	Leu Glu Glu Arg Asp Trp Leu Pro Gly Gln Pro Val Leu Glu Asn Leu	
	275 280 285	
30	TCC CAG AGC ATA CAG CTC AGC AAA AAG ACA GTG TTT GTG ATG ACA CAG	912
	Ser Gln Ser Ile Gln Leu Ser Lys Lys Thr Val Phe Val Met Thr Gln	
	290 295 300	
35	AAA TAT GCT AAG ACT GAG AGT TTT AAG ATG GCA TTT TAT TTG TCT CAT	960
	Lys Tyr Ala Lys Thr Glu Ser Phe Lys Met Ala Phe Tyr Leu Ser His	
	305 310 315 320	
40	CAG AGG CTC CTG GAT GAA AAA GTG GAT GTG ATT ATC TTG ATA TTC TTG	1008
	Gln Arg Leu Leu Asp Glu Lys Val Asp Val Ile Ile Leu Ile Phe Leu	
	325 330 335	
	GAA AGA CCT CTT CAG AAG TCT AAG TTT CTT CAG CTC AGG AAG AGA CTC	1056
	Glu Arg Pro Leu Gln Lys Ser Lys Phe Leu Gln Leu Arg Lys Arg Leu	
	340 345 350	
45	TGC AGG AGC TCT GTC CTT GAG TGG CCT GCA AAT CCA CAG GCT CAC CCA	1104
	Cys Arg Ser Ser Val Leu Glu Trp Pro Ala Asn Pro Gln Ala His Pro	
	355 360 365	
50	TAC TTC TGG CAG TGC CTG AAA AAT GCC CTG ACC ACA GAC AAT CAT GTG	1152
	Tyr Phe Trp Gln Cys Leu Lys Asn Ala Leu Thr Thr Asp Asn His Val	
	370 375 380	
55	GCT TAT AGT CAA ATG TTC AAG GAA ACA GTC TAGCTCTCTG AAGAATGTCA	1202
	Ala Tyr Ser Gln Met Phe Lys Glu Thr Val	
	385 390	

CCACCTAGGA CATGCCTTGG TACCTGAAGT TTTCATAAAG GTTTCATAA ATGAAGGTCT 1262
 GAATTTTTC TAACAGTTGT CATGGCTCAG ATTGGTGGGA AATCATCAAT ATATGCCTAA 1322
 5 GAAATTAAGA AGGGGAGACT GATAGAAGAT AATTTCTTTC TTCATGTGCC ATGCTCAGTT 1382
 AAATATTTCC CCTAGCTCAA ATCTGAAAA CTGTGCCCTAG GAGACAACAC AAGGCTTTGA 1442
 10 TTTATCTGCA TACAATTGAT AAGAGCCACA CATCTGCCCT GAAGAAGTAC TAGTAGTTTT 1502
 AGTAGTAGGG TAAAAATTAC ACAAGCTTTC TCCTCTCTCTG ATACTGAACT GTACCAGAGT 1562
 TCAATGAAAT AAAAGCCCAG AGAACTTCTC AGTAAATGGT TTCATTATCA TGTAGTATCC 1622
 15 ACCATGCAAT ATGCCACAAA ACCGCTACTG GTACAGGACA GCTGGTAGCT GCTTCAAGGC 1682
 CTCTTATCAT TTTCTTGGGG CCCATGGAGC GGTCTCTCTG GAAAAAGGGA AGGTTTTTTT 1742
 20 TGGCCATCCA TGAA 1756
 SPEIPWNSLPPEVFEGMPPNKLKSLAKNGLKSFFWDRLQLLKHLEILDLSHNQLTKVPERLANCSKSLTTLLK
 HNQIRQLTKYFLEDALQLRYLDISSNKIQVIQKTSFPENVLNNLEMLVLHHRFLCNCDAVAFVWVNNHTDVTIP
 YLATDVT CVGPGAHKGQSVISLDLYTCELDLTNLILFSVSISSVLFMLVVMTTSHLFFWDMWYIYFVKAKIKGY
 25 PASAIPWSPCYDAFIVYDTKNSAVTEWVLQELVAKLEDPREKHFNLCLEERDWLPQGPVLENLSQSIQLSKKTVF
 VMTQKYAKTFSEFKMAFYLSHQRLDDEKVDVILLIFLERPLQSKFLQLRKRLCRSSVLEWPANPQAHYPFWQCLK
 NALTTDNHVAYSQMFKETV

Table 7: Nucleotide and amino acid sequences of a mammalian, e.g., primate, human, DNAX TcII like Receptor 7 (DTLR7).

upstream (SEQ ID NO: 15 and 16):

5	G AAT TCC AGA CTT ATA AAC TTG AAA AAT CTC TAT TTG GCC TGG AAC	46
	Asn Ser Arg Leu Ile Asn Leu Lys Asn Leu Tyr Leu Ala Trp Asn	
	1 5 10 15	
10	TGC TAT TTT AAC AAA GTT TGC GAG AAA ACT AAC ATA GAA GAT GGA GTA	94
	Cys Tyr Phe Asn Lys Val Cys Glu Lys Thr Asn Ile Glu Asp Gly Val	
	20 25 30	
15	TTT GAA ACG CTG ACA AAT TTG GAG TTG CTA TCA CTA TCT TTC AAT TCT	142
	Phe Glu Thr Leu Thr Asn Leu Glu Leu Leu Ser Leu Ser Phe Asn Ser	
	35 40 45	
20	CTT TCA CAT GTG CCA CCC AAA CTG CCA AGC TCC CTA CGC AAA CTT TTT	190
	Leu Ser His Val Pro Pro Lys Leu Pro Ser Ser Leu Arg Lys Leu Phe	
	50 55 60	
	CTG AGC AAC ACC CAG ATC AAA TAC ATT AGT GAA GAA GAT TTC AAG GGA	238
	Leu Ser Asn Thr Gln Ile Lys Tyr Ile Ser Glu Glu Asp Phe Lys Gly	
	65 70 75	
25	TTG ATA AAT TTA ACA TTA CTA GAT TTA AGC GGG AAC TGT CCG AGG TGC	286
	Leu Ile Asn Leu Thr Leu Leu Asp Leu Ser Gly Asn Cys Pro Arg Cys	
	80 85 90 95	
30	TTC AAT GCC CCA TTT CCA TGC CTG CCT TGT GAT GGT GGT GCT TCA ATT	334
	Phe Asn Ala Pro Phe Pro Cys Val Pro Cys Asp Gly Gly Ala Ser Ile	
	100 105 110	
35	AAT ATA GAT CGT TTT GCT TTT CAA AAC TTG ACC CAA CTT CGA TAC CTA	382
	Asn Ile Asp Arg Phe Ala Phe Gln Asn Leu Thr Gln Leu Arg Tyr Leu	
	115 120 125	
40	AAC CTC TCT AGC ACT TCC CTC AGG AAG ATT AAT GCT GCC TGG TTT AAA	430
	Asn Leu Ser Ser Thr Ser Leu Arg Lys Ile Asn Ala Ala Trp Phe Lys	
	130 135 140	
	AAT ATG CCT CAT CTG AAG GTG CTG GAT CTT GAA TTC AAC TAT TTA GTG	478
	Asn Met Pro His Leu Lys Val Leu Asp Leu Glu Phe Asn Tyr Leu Val	
	145 150 155	
45	GGA GAA ATA GCC TCT GGG GCA TTT TTA ACG ATG CTG CCC CGC TTA GAA	526
	Gly Glu Ile Ala Ser Gly Ala Phe Leu Thr Met Leu Pro Arg Leu Glu	
	160 165 170 175	
50	ATA CTT GAC TTG TCT TTT AAC TAT ATA AAG GGG AGT TAT CCA CAG CAT	574
	Ile Leu Asp Leu Ser Phe Asn Tyr Ile Lys Gly Ser Tyr Pro Gln His	
	180 185 190	

	ATT AAT ATT TCC AGA AAC TTC TCT AAA CTT TTG TCT CTA CGG GCA TTG	622
	Ile Asn Ile Ser Arg Asn Phe Ser Lys Leu Leu Ser Leu Arg Ala Leu	
	195 200 205	
5	CAI TTA AGA GGT TAT GTG TTC CAG GAA CTC AGA GAA GAT GAT TTC CAG	670
	His Leu Arg Gly Tyr Val Phe Gln Glu Leu Arg Glu Asp Asp Phe Gln	
	210 215 220	
10	CCC CTG ATG CAG CTT CCA AAC TTA TCG ACT ATC AAC TTG GGT ATT AAT	718
	Pro Leu Met Gln Leu Pro Asn Leu Ser Thr Ile Asn Leu Gly Ile Asn	
	225 230 235	
15	TTT ATT AAG CAA ATC GAT TTC AAA CTT TTC CAA AAT TTC TCC AAT CTG	766
	Phe Ile Lys Gln Ile Asp Phe Lys Leu Phe Gln Asn Phe Ser Asn Leu	
	240 245 250 255	
20	GAA ATT ATT TAC TTG TCA GAA AAC AGA ATA TCA CCG TTG GTA AAA GAT	814
	Glu Ile Ile Tyr Leu Ser Glu Asn Arg Ile Ser Pro Leu Val Lys Asp	
	260 265 270	
	ACC CGG CAG AGT TAT GCA AAT AGT TCC TCT TTT CAA CGT CAT ATC CGG	862
	Thr Arg Gln Ser Tyr Ala Asn Ser Ser Ser Phe Gln Arg His Ile Arg	
	275 280 285	
25	AAA CGA CGC TCA ACA GAT TTT GAG TTT GAC CCA CAT TCG AAC TTT TAT	910
	Lys Arg Arg Ser Thr Asp Phe Glu Phe Asp Pro His Ser Asn Phe Tyr	
	290 295 300	
30	CAT TTC ACC CGT CCT TTA ATA AAG CCA CAA TGT GCT GCT TAT GGA AAA	958
	His Phe Thr Arg Pro Leu Ile Lys Pro Gln Cys Ala Ala Tyr Gly Lys	
	305 310 315	
35	GCC TTA GAT TTA AGC CTC AAC AGT ATT TTC TT	990
	Ala Leu Asp Leu Ser Leu Asn Ser Ile Phe	
	320 325	
40	NSRLINLKNLYLAWNCYFNKVCEKTNIEDGVFETLTNLELLSLSFNSLSHVPPKLPSSLRKLFSLNTQIKYISE EDFKGLINLTLLDLSGNCPRCFNAPFPCVFCDDGGASINIDRFQNLTLQRLYNLSSTSLRKINAAWFKNMPHL KVLDFEFNYLVGEIASGAFITMLPRLEILOLSFNFIKGSYPQHINISRNFSKLLSLRALHLRGYVFOELREDDF QPLMQLPNLSTINLGINFIKQIDFKLFQNFSLNLEIIYLSNRIPLVKDTRQSYANSSSFQRHIRKRRTDFF DPHSNFYHETRPLIKPQCAAYGKALDLSINSIF	
45	downstream (SEQ ID NO: 17 and 18):	
	CAG TCT CTT TCC ACA TCC CAA ACT TTC TAT GAT GCT TAC ATT TCT TAT	48
	Gln Ser Leu Ser Thr Ser Gln Thr Phe Tyr Asp Ala Tyr Ile Ser Tyr	
	1 5 10 15	
50	GAC ACC AAA GAT GCC TCT GTT ACT GAC TGG GTG ATA AAT GAG CTG CGC	96
	Asp Thr Lys Asp Ala Ser Val Thr Asp Trp Val Ile Asn Glu Leu Arg	
	20 25 30	

	TAC CAC CTT GAA GAG AGC CGA GAC AAA AAC GTT CTC CTT TGT CTA GAG	144
	Tyr His Leu Glu Glu Ser Arg Asp Lys Asn Val Leu Leu Cys Leu Glu	
	35 40 45	
5	GAG AGG GAT TGG GAC CCG GGA TTG GCC ATC ATC GAC AAC CTC ATG CAG	192
	Glu Arg Asp Trp Asp Pro Gly Leu Ala Ile Ile Asp Asn Leu Met Gln	
	50 55 60	
10	AGC ATC AAC CAA AGC AAG AAA ACA GTA TTT GTT TTA ACC AAA AAA TAT	240
	Ser Ile Asn Gln Ser Lys Lys Thr Val Phe Val Leu Thr Lys Lys Tyr	
	65 70 75 80	
15	GCA AAA AGC TGG AAC TTT AAA ACA GCT TTT TAC TTG GGC TTG CAG AGG	288
	Ala Lys Ser Trp Asn Phe Lys Thr Ala Phe Tyr Leu Gly Leu Gln Arg	
	85 90 95	
20	CTA ATG GGT GAS AAC ATG GAT GTG ATT ATA TTT ATC CTG CTG GAG CCA	336
	Leu Met Gly Glu Asn Met Asp Val Ile Ile Phe Ile Leu Leu Glu Pro	
	100 105 110	
25	GTG TTA CAG CAT TCT CCG TAT TTG AGG CTA CCG CAG CCG ATC TGT AAG	384
	Val Leu Gln His Ser Pro Tyr Leu Arg Leu Arg Gln Arg Ile Cys Lys	
	115 120 125	
30	AGC TCC ATC CTC CAG TGG CCT GAC AAC CCG AAG GCA GAA AGG TTG TTT	432
	Ser Ser Ile Leu Gln Trp Pro Asp Asn Pro Lys Ala Glu Arg Leu Phe	
	130 135 140	
35	TGG CAA ACT CTG AGA AAT GTG GTC TTG ACT GAA AAT GAT TCA CCG TAT	480
	Trp Gln Thr Leu Arg Asn Val Val Leu Thr Glu Asn Asp Ser Arg Tyr	
	145 150 155 160	
40	AAC AAT ATG TAT GTC GAT TCC ATT AAG CAA TAC TAACTGACGT TAAGTCATGA	533
	Asn Asn Met Tyr Val Asp Ser Ile Lys Gln Tyr	
	165 170	
45	TTTCGCGCCA TAATAAGAT GCAAAGGAAT GACATTTCCG TATTAGTTAT CTATTGCTAC	593
	GGTAACCAAA TTAATCCCAA AAACCTTACG TCGGTTTCAA AACACCACA TTCTGCTGGC	653
	CCCACAGITT TTGAGGGTCA GGAGTCCAGG CCCAGCATAA CTGGGTCTTC TGCTTCAGGG	713
	TGTCTCCAGA GGCTGCAATG TAGGTGTTCA CCAGAGACAT AGGCATCACT GGGGTCACAC	773
50	TCCATGTGGT TGTTTTCTGG ATTCAATTCC TCCTGGGCTA TTGGCCAAAG GCTATACTCA	833
	TGTAAGCCAT GCGAGCCTAT CCCACAACGG CAGCTTGCTT CATCAGAGCT AGCAAAAAAG	893
	AGAGGTTGCT AGCAAGATGA AGTCACAATC TTTTGTAAAT GAAATCAAAA AGTGATATCT	953
	CATCACTTTG GCCATATTCT ATTTGTTAGA AGTAAACCAC AGGTCCCACC AGCTCCATGG	1013
	GAGTGACCAC CTCAGTCCAG GGAAAACAGC TGAAGACCAA GATGGTGAGC TCIGATTGCT	1073
55	TCAGTTGGTC ATCAACTATT TTCCCTTGAC TGCTGTCCTG GGATGGCCGG CTATCTTGAT	1133

GGATAGATTG TGAATATCAG GAGGCCAGGG ATCACTGTGG ACCATCTTAG CAGTTGACCT 1193
 AACACATCTT CTTTCAATA TCTAAGAACT TTTGCCACTG TGAATAATGG TCCTAATATT 1253
 5 AAGCTGTTGT TTATATTAT CATATATCTA TGGCTACATG GTTATATTAT GCTGTGGTTG 1313
 CGTTCGGTTT TATTTACAGT TGCTTTTACA AATATTTGCT GTAACATTTG ACTTCTAAGG 1373
 10 TTTAGATGCC ATTAAGAAGC TGAGATGGAT AGCTTTTAAA GCATCTTTTA CTTCTTACCA 1433
 TTTTITAAAA GTATGCAGCT AAATTCGAAG CTTTGGTCT ATATIGTTAA TTGCCATTGC 1493
 15 TGTAAATCTT AAAATGAATG AATAAAATG TTTCATTTTA AAAAAAAAAA AAAAAAAAAA 1553
 AAAA 1557
 QSLSTSOTFYDAYISYDTKASVTDWVINELRYHLEESFDKNVLLCLEERDWDPLAIDNLMQSINQSKKTVFV
 LTKKYAKSWNFKTA FYLGLQRLMGENMDVIIIFILLEPVLQHSPLYRLRQRICKSSILQWPDNPKAERLFWQTLRN
 20 VVLTENDSRYNMYVDSIKQY

Further primate, e.g., human, DTLR7 sequence (SEQ ID NO: 36 and 37).

25 atg ctg acc tgc att ttc ctg cta ata tct ggt tcc tgt gag tta tgc 48
 Met Leu Thr Cys Ile Phe Leu Leu Ile Ser Gly Ser Cys Glu Leu Cys
 -15 -10 -5
 30 gcc gaa gea aat ttt tct aga agc tat cct tgt gat gag aaa aag caa 96
 Ala Glu Glu Asn Phe Ser Arg Ser Tyr Pro Cys Asp Glu Lys Lys Gln
 -1 1 5 10 15
 35 aat gac tca gtt att gca gag tgc agc aat cgt cga cta cag gaa gtt 144
 Asn Asp Ser Val Ile Ala Glu Cys Ser Asn Arg Arg Leu Gln Glu Val
 20 25 30
 40 ccc caa acg gtg ggc aaa tat gtg aca gaa cta gac ctg tct gat aat 192
 Pro Gln Thr Val Gly Lys Tyr Val Thr Glu Leu Asp Leu Ser Asp Asn
 35 40 45
 45 ttc atc aca cac ata acg aat gaa tca ttt caa ggg ctg caa aat ctc 240
 Phe Ile Thr His Ile Thr Asn Glu Ser Phe Gln Gly Leu Gln Asn Leu
 50 55 60
 50 act aaa ata aat cta aac cac aac ccc aat gta cag cac cag aac gga 288
 Thr Lys Ile Asn Leu Asn His Asn Pro Asn Val Gln His Gln Asn Gly
 65 70 75
 55 aat ccc ggt ata caa tca aat ggc ttg aat atc aca gac ggg gca ttc 336
 Asn Pro Gly Ile Gln Ser Asn Gly Leu Asn Ile Thr Asp Gly Ala Phe
 80 85 90 95
 55 ctc aac cta aaa aac cta agg gag tta ctg ctt gaa gac aac cag tta 384
 Leu Asn Leu Lys Asn Leu Arg Glu Leu Leu Leu Glu Asp Asn Gln Leu
 100 105 110

	ccc	caa	ata	ccc	tct	ggt	ttg	cca	gag	tct	ttg	aca	gaa	ctt	agt	cta	432
	Pro	Gln	Ile	Pro	Ser	Gly	Leu	Pro	Glu	Ser	Leu	Thr	Glu	Leu	Ser	Leu	
				115					120					125			
5	att	caa	aac	aat	ata	tac	aac	ata	act	aaa	gag	ggc	att	tca	aga	ctt	480
	Ile	Gln	Asn	Asn	Ile	Tyr	Asn	Ile	Thr	Lys	Glu	Gly	Ile	Ser	Arg	Leu	
			130				135						140				
10	ata	aac	ttg	aaa	aat	ctc	tat	ttg	gcc	tgg	aac	tgc	tat	ttt	aac	aaa	528
	Ile	Asn	Leu	Lys	Asn	Leu	Tyr	Leu	Ala	Trp	Asn	Cys	Tyr	Phe	Asn	Lys	
		145					150					155					
15	gtt	tgc	gag	aaa	act	aac	ata	gaa	gat	gga	gta	ttt	gaa	acg	ctg	aca	576
	Val	Cys	Glu	Lys	Thr	Asn	Ile	Glu	Asp	Gly	Val	Phe	Glu	Thr	Leu	Thr	
	160					165				170						175	
20	aat	ttg	gag	ttg	cta	tca	cta	tct	ttc	aat	tct	ctt	tca	cat	gtg	cca	624
	Asn	Leu	Glu	Leu	Leu	Ser	Leu	Ser	Phe	Asn	Ser	Leu	Ser	His	Val	Pro	
					180					185					190		
25	ccc	aaa	ctg	cca	agc	tcc	cta	cgc	aaa	ctt	ttt	ctg	agc	aac	acc	cag	672
	Pro	Lys	Leu	Pro	Ser	Ser	Leu	Arg	Lys	Leu	Phe	Leu	Ser	Asn	Thr	Gln	
				195					200					205			
30	atc	aaa	tac	att	agt	gaa	gaa	gat	ttc	aag	gga	ttg	ata	aat	tta	aca	720
	Ile	Lys	Tyr	Ile	Ser	Glu	Glu	Asp	Phe	Lys	Gly	Leu	Ile	Asn	Leu	Thr	
			210					215					220				
35	tta	cta	gat	tta	agc	ggg	aac	tgt	ccg	agg	tgc	ttc	aat	gcc	cca	ttt	768
	Leu	Leu	Asp	Leu	Ser	Gly	Asn	Cys	Pro	Arg	Cys	Phe	Asn	Ala	Pro	Phe	
		225					230					235					
40	cca	tgc	gtg	cct	tgt	gat	ggt	ggt	gct	tca	att	aat	ata	gat	cgt	ttt	816
	Pro	Cys	Val	Pro	Cys	Asp	Gly	Gly	Ala	Ser	Ile	Asn	Ile	Asp	Arg	Phe	
	240					245					250				255		
45	gct	ttt	caa	aac	ttg	acc	caa	ctt	cga	tac	cta	aac	ctc	tct	agc	act	864
	Ala	Phe	Gln	Asn	Leu	Thr	Gln	Leu	Arg	Tyr	Leu	Asn	Leu	Ser	Ser	Thr	
					260					265					270		
50	tcc	ctc	agg	aag	att	aat	gct	gcc	tgg	ttt	aaa	aat	atg	cct	cat	ctg	912
	Ser	Leu	Arg	Lys	Ile	Asn	Ala	Ala	Trp	Phe	Lys	Asn	Met	Pro	His	Leu	
				275					280					285			
55	aag	gtg	ctg	gat	ctt	gaa	ttc	aac	tat	tta	gtg	gga	gaa	ata	gcc	tct	960
	Lys	Val	Leu	Asp	Leu	Glu	Phe	Asn	Tyr	Leu	Val	Gly	Glu	Ile	Ala	Ser	
			290					295					300				
60	ggg	gca	ttt	tta	acg	atg	ctg	ccc	cgc	tta	gaa	ata	ctt	gac	ttg	tct	1008
	Gly	Ala	Phe	Leu	Thr	Met	Leu	Pro	Arg	Leu	Glu	Ile	Leu	Asp	Leu	Ser	
		305					310					315					
65	ttt	aac	tat	ata	aag	ggg	agt	tat	cca	cag	cat	att	aat	att	tcc	aga	1056
	Phe	Asn	Tyr	Ile	Lys	Gly	Ser	Tyr	Pro	Gln	His	Ile	Asn	Ile	Ser	Arg	
		320				325					330					335	

	aac ttc tct aaa ctt ttg tct cta cgg gca ttg cat tta aga ggt tat	1104
	Asn Phe Ser Lys Leu Leu Ser Leu Arg Ala Leu His Leu Arg Gly Tyr	
	340 345 350	
5	gtg ttc cag gaa ctg aga gaa gat gat ttc cag ccc ctg atg cag ctt	1152
	Val Phe Gln Glu Leu Arg Glu Asp Asp Phe Gln Pro Leu Met Gln Leu	
	355 360 365	
10	cca aac tta tcg act atc aac ttg ggt att aat ttt att aag caa atc	1200
	Pro Asn Leu Ser Thr Ile Asn Leu Gly Ile Asn Phe Ile Lys Gln Ile	
	370 375 380	
15	gat ttc aaa ctt ttc caa aat ttc tcc aat ctg gaa att att tac ttg	1248
	Asp Phe Lys Leu Phe Gln Asn Phe Ser Asn Leu Glu Ile Ile Tyr Leu	
	385 390 395	
20	tca gaa aac aga ata tca ccg ttg gta aaa gat acc cgg cag agt tat	1296
	Ser Glu Asn Arg Ile Ser Pro Leu Val Lys Asp Thr Arg Gln Ser Tyr	
	400 405 410 415	
25	gca aat agt tcc tct ttt caa cgt cat atc cgg aaa cga cgc tca aca	1344
	Ala Asn Ser Ser Ser Phe Gln Arg His Ile Arg Lys Arg Arg Ser Thr	
	420 425 430	
30	gat ttt gag ttt gac cca cat tcg aac ttt tat cat ttc acc cgt cct	1392
	Asp Phe Glu Phe Asp Pro His Ser Asn Phe Tyr His Phe Thr Arg Pro	
	435 440 445	
35	tta ata aag cca caa tgt gct gct tat gga aaa gcc tta gat tta agc	1440
	Leu Ile Lys Pro Gln Cys Ala Ala Tyr Gly Lys Ala Leu Asp Leu Ser	
	450 455 460	
40	ctc aac agt att ttc ttc att ggg cca aac caa ttt gaa aat ctt cct	1488
	Leu Asn Ser Ile Phe Phe Ile Gly Pro Asn Gln Phe Glu Asn Leu Pro	
	465 470 475	
45	gac att gcc tgt tta aat ctg tct gca aat agc aat gct caa gtg tta	1536
	Asp Ile Ala Cys Leu Asn Leu Ser Ala Asn Ser Asn Ala Gln Val Leu	
	480 485 490 495	
50	agt gga act gaa ttt tca gcc att cct cat gtc aaa tat ttg gat ttg	1584
	Ser Gly Thr Glu Phe Ser Ala Ile Pro His Val Lys Tyr Leu Asp Leu	
	500 505 510	
55	aca aac aat aga cta gac ttt gat aat gct agt gct ctt act gaa ttg	1632
	Thr Asn Asn Arg Leu Asp Phe Asp Asn Ala Ser Ala Leu Thr Glu Leu	
	515 520 525	
60	tcc gac ttg gaa gtt cta gat ctc agc tat aat tca cac tat ttc aga	1680
	Ser Asp Leu Glu Val Leu Asp Leu Ser Tyr Asn Ser His Tyr Phe Arg	
	530 535 540	
65	ata gca ggc gta aca cat cat cta gaa ttt att caa aat ttc aca aat	1728
	Ile Ala Gly Val Thr His His Leu Glu Phe Ile Gln Asn Phe Thr Asn	
	545 550 555	
70	cta aaa gtt tta aac ttg agc cac aac aac att tat act tta aca gat	1776
	Leu Lys Val Leu Asn Leu Ser His Asn Asn Ile Tyr Thr Leu Thr Asp	

	560		565		570		575	
	aag tat aac ctg gaa agc aag tcc ctg gta gaa tta gtt ttc agt ggc							1824
5	Lys Tyr Asn Leu Glu Ser Lys Ser Leu Val Glu Leu Val Phe Ser Gly							
		580		585		590		
	aat cgc ctt gac att ttg tgg aat gat gat gac aac agg tat atc tcc							1872
	Asn Arg Leu Asp Ile Leu Trp Asn Asp Asp Asp Asn Arg Tyr Ile Ser							
10		595		600		605		

	att ttc aaa ggt ctc aag aat ctg aca cgt ctg gat tta tcc ctt aat	1920
	Ile Phe Lys Gly Leu Lys Asn Leu Thr Arg Leu Asp Leu Ser Leu Asn	
	610 615 620	
5	agg ctc aag cac atc cca aat gaa gca ttc ctt aat ttg cca gcg agt	1968
	Arg Leu Lys His Ile Pro Asn Glu Ala Phe Leu Asn Leu Pro Ala Ser	
	625 630 635	
10	ctc act gaa cta cat ata aat gat aat atg tta aag ttt ttt aac tgg	2016
	Leu Thr Glu Leu His Ile Asn Asp Asn Met Leu Lys Phe Phe Asn Trp	
	640 645 650 655	
15	aca tta ctc cag cag ttt cct cgt ctc gag ttg ctt gac tta cgt gga	2064
	Thr Leu Leu Gln Gln Phe Pro Arg Leu Glu Leu Leu Asp Leu Arg Gly	
	660 665 670	
20	aac aaa cta ctc ttt tta act gat agc cta tct gac ttt aca tct tcc	2112
	Asn Lys Leu Leu Phe Leu Thr Asp Ser Leu Ser Asp Phe Thr Ser Ser	
	675 680 685	
25	ctt cgg aca ctg ctg ctg agt cat aac agg att tcc cac cta ccc tct	2160
	Leu Arg Thr Leu Leu Leu Ser His Asn Arg Ile Ser His Leu Pro Ser	
	690 695 700	
30	ggc ttt ctt tct gaa gtc agt agt ctg aag cac ctc gat tta agt tcc	2208
	Gly Phe Leu Ser Glu Val Ser Ser Leu Lys His Leu Asp Leu Ser Ser	
	705 710 715	
35	aat ctg cta aaa aca atm aac aaa tcc gca ctt gaa act aag acc acc	2256
	Asn Leu Leu Lys Thr Xaa Asn Lys Ser Ala Leu Glu Thr Lys Thr Thr	
	720 725 730 735	
40	acc aaa tta tct atg ttg gaa cta cac gga aac ccc ttt gaa tgc acc	2304
	Thr Lys Leu Ser Met Leu Glu Leu His Gly Asn Pro Phe Glu Cys Thr	
	740 745 750	
45	tgt gac att gga gat ttc cga aga tgg atg gat gaa cat ctg aat gtc	2352
	Cys Asp Ile Gly Asp Phe Arg Arg Trp Met Asp Glu His Leu Asn Val	
	755 760 765	
50	aaa att ccc aga ctg gta gat gtc att tgt gcc agt cct ggg gat caa	2400
	Lys Ile Pro Arg Leu Val Asp Val Ile Cys Ala Ser Pro Gly Asp Gln	
	770 775 780	
55	aga ggg aag agt att gtg agt ctg gag cta aca act tgt gtt tca gat	2448
	Arg Gly Lys Ser Ile Val Ser Leu Glu Leu Thr Thr Cys Val Ser Asp	
	785 790 795	
60	gtc act gca gtg ata tta ttt ttc ttc acg ttc ttt atc acc acc atg	2496
	Val Thr Ala Val Ile Leu Phe Phe Phe Thr Phe Phe Ile Thr Thr Met	
	800 805 810 815	
65	gtt atg ttg gct gcc ctg gct cac cat ttg ttt tac tgg gat gtt tgg	2544
	Val Met Leu Ala Ala Leu Ala His His Leu Phe Tyr Trp Asp Val Trp	
	820 825 830	

	ttt ata tat aat gtg tgt tta gct aag tta aaa ggc tac agg tct ctt	2592
	Phe Ile Tyr Asn Val Cys Leu Ala Lys Leu Lys Gly Tyr Arg Ser Leu	
	835 840 845	
5	tcc aca tcc caa act ttc tat gat gct tac att tct tat gac acc aaa	2640
	Ser Thr Ser Gln Thr Phe Tyr Asp Ala Tyr Ile Ser Tyr Asp Thr Lys	
	850 855 860	
10	gat gcc tct gtt act gac tgg gtg ata aat gag ctg cgc tac cac ctt	2688
	Asp Ala Ser Val Thr Asp Trp Val Ile Asn Glu Leu Arg Tyr His Leu	
	865 870 875	
15	gaa gag agc cga gac aaa aac gtt ctc ctt tgt cta gag gag agg gat	2736
	Glu Glu Ser Arg Asp Lys Asn Val Leu Leu Cys Leu Glu Glu Arg Asp	
	880 885 890 895	
20	tgg gac ccg gga ttg gcc atc atc gac aac ctc atg cag agc atc aac	2784
	Trp Asp Pro Gly Leu Ala Ile Ile Asp Asn Leu Met Gln Ser Ile Asn	
	900 905 910	
	caa agc aag aaa aca gta ttt gtt tta acc aaa aaa tat gca aaa agc	2832
	Gln Ser Lys Lys Thr Val Phe Val Leu Thr Lys Lys Tyr Ala Lys Ser	
	915 920 925	
25	tgg aac ttt aaa aca gct ttt tac ttg gcc ttg cag agg cta atg ggt	2880
	Trp Asn Phe Lys Thr Ala Phe Tyr Leu Ala Leu Gln Arg Leu Met Gly	
	930 935 940	
30	gag aac atg gat gtg att ata ttt atc ctg ctg gag cca gtg tta cag	2928
	Glu Asn Met Asp Val Ile Ile Phe Ile Leu Leu Glu Pro Val Leu Gln	
	945 950 955	
35	cat tct ccg tat ttg agg cta cgg cag cgg atc tgt aag agc tcc atc	2976
	His Ser Pro Tyr Leu Arg Leu Arg Gln Arg Ile Cys Lys Ser Ser Ile	
	960 965 970 975	
40	ctc cag tgg cct gac aac ccg aag gca gaa ggc ttg ttt tgg caa act	3024
	Leu Gln Trp Pro Asp Asn Pro Lys Ala Glu Gly Leu Phe Trp Gln Thr	
	980 985 990	
	ctg aga aat gtg gtc ttg act gaa aat gat tca cgg tat aac aat atg	3072
	Leu Arg Asn Val Val Leu Thr Glu Asn Asp Ser Arg Tyr Asn Asn Met	
	995 1000 1005	
45	tat gtc gat tcc att aag caa tac taa	3099
	Tyr Val Asp Ser Ile Lys Gln Tyr	
	1010 1015	

MLTCIFLLISGSCELCAEENFSRSYPCDEKKQND SVIAECSNRRLQEVPTVGKYVTELDLSDNFIITHI
TNESFQGLQNLTKINLNHNPNVQHONGNPGIQSNGLNITDGAPLNKLNRELLLEDNQLPQIPSGLPES
LTELSLIQNNIYNITKEGISRLINLKNLYLAWNCYFNKVCEKTNIEDGVFETLTNLELLSLSFNLSFV
PPKLPSSLRKLFLSNTQIKYIS3EDFKGLINLTLLDLSGNCPRCFNAPFPCVPCDGGASINIDRFQFN
5 LTQLRYLNLSSTSLRKINAAWFKNMPHLKVLDLEFNLYVGELASGAFITMLPRLEILDLSFNITKGSYP
QHINISRNFSKLLSLRALHLRGYVFQELREDDFQPLMQLPNLSTINLGINFIKQIDFKLFQNFNLEII
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IFFIGPNQFENLPDIACLNLSANSNAQVLSGTEFSAIPHVKYLDLTNNRLDFDNASALTELSDLEVLDL
SYNSHYFRIAGVTHHLEFIQNFMTLKVNLSHNNIYTLTDKYNLESKSLVELVFSGNRLDILWNDDNR
10 YISIFKGLKNLTRLDLSLNRLKHIPNEAFLNLPASLTELHINDNMLKFFNWTLQFPRLELLDLRGNK
LLFLTDSLSDFTSSLRTLLLSHNRI SHLPSGFLSEVSSLKHLDLSSNLLKTINKSALETKTTTKLSMLE
LHGNPFECTCDIGDFRRWMDEHLNVKIPRLVDVICASPGDQRGKSIVSLELTTCVSDVTAVILFFFTFF
ITTMVMLAALAHHLFYWDVWFIYNVCLAKLKGYSLSSTSQTIFYDAYISYDTKASVTDWVINELRYHLE
ESRDKNVLLCLEERDWDPLAIIDNLMQSTINQSKKTFFVLTKKYAKSWNFKTA FYLALQRLMGENMDVI
15 IFILLEPVLQHSPLYRLRQRICKSSILQWPDNPKAEGFLWQTLRNVVLTEENDSRYNMYVDSIKQY

Table 8: Partial nucleotide and amino acid sequences (see SEQ ID NO: 19 and 20) of a mammalian, e.g., primate, human, DNAX Toll like Receptor 8 (DTRLR8).

5	AAT GAA TTG ATC CCC AAT CTA GAG AAG GAA GAT GGT TCT ATC TTG ATT Asn Glu Leu Ile Pro Asn Leu Glu Lys Glu Asp Gly Ser Ile Leu Ile 1 5 10 15	48
10	TGC CTT TAT GAA AGC TAC TTT GAC CCT GGC AAA AGC ATT AGT GAA AAT Cys Leu Tyr Glu Ser Tyr Phe Asp Pro Gly Lys Ser Ile Ser Glu Asn 20 25 30	96
15	ATT GTA AGC TTC ATT GAG AAA AGC TAT AAG TCC ATC TTT GTT TTG TCC Ile Val Ser Phe Ile Glu Lys Ser Tyr Lys Ser Ile Phe Val Leu Ser 35 40 45	144
20	CCC AAC TTT GTC CAG AAT GAG TGG TGC CAT TAT GAA TTC TAC TTT GCC Pro Asn Phe Val Gln Asn Glu Trp Cys His Tyr Glu Phe Tyr Phe Ala 50 55 60	192
25	CAC CAC AAT CTC TTC CAT GAA AAT TCT GAT CAC ATA ATT CTT ATC TTA His His Asn Leu Phe His Glu Asn Ser Asp His Ile Ile Leu Ile Leu 65 70 75 80	240
30	CTG GAA CCC ATT CCA TTC TAT TGC ATT CCC ACC AGG TAT CAT AAA CTG Leu Glu Pro Ile Pro Phe Tyr Cys Ile Pro Thr Arg Tyr His Lys Leu 85 90 95	288
35	GAA GCT CTC CTG GAA AAA AAA GCA TAC TTG GAA TGG CCC AAG GAT AGG Glu Ala Leu Leu Glu Lys Lys Ala Tyr Leu Glu Trp Pro Lys Asp Arg 100 105 110	336
40	CGT AAA TGT GGG CTT TTC TGG GCA AAC CTT CGA GCT GCT GTT AAT GTT Arg Lys Cys Gly Leu Phe Trp Ala Asn Leu Arg Ala Ala Val Asn Val 115 120 125	384
45	AAT GTA TTA GCC ACC AGA GAA ATG TAT GAA CTG CAG ACA TTC ACA GAG Asn Val Leu Ala Thr Arg Glu Met Tyr Glu Leu Gln Thr Phe Thr Glu 130 135 140	432
50	TTA AAT GAA GAG TCT CGA GGT TCT ACA ATC TCT CTG ATG AGA ACA GAC Leu Asn Glu Glu Ser Arg Gly Ser Thr Ile Ser Leu Met Arg Thr Asp 145 150 155 160	480
55	TGT CTA TAAAATCCCA CAGTCCTTGG GAAGTTGGGG ACCACATACA CTGTTGGGAT Cys Leu	536
60	GTACATTGAT ACAACCTTTA TGATGGCAAT TTGACAATAT TTATTAAAT AAAAAATGGT TATTCCTTC AAAAAAAAAA AAAAAAAAAA AAA	596 628
65	NELIPNLEKEDGSILICLYESYFDEGKSISENIVSFIKSYKSIFVLSPNFVQNEWCHYEFYFAHHNLFHENS HIILILLEPIPFYCIPTRYHKLEALLEKKAYLEWPKDRRKGLFWANLRAAVNVNVLATREMYELQTFTELNI SRGSTISLMRTDCL	

additional primate, e.g., human sequence (SEQ ID NO: 31 and 32); nucleotides 4 and 23 designated C, may be A, C, G, or T; nucleotide 845 designated C, may be C or T:

5	C TCC GAT GCC AAG ATT CGG CAC CAG GCA TAT TCA GAG GTC ATG ATG	46
	Ser Asp Ala Lys Ile Arg His Gln Ala Tyr Ser Glu Val Met Met	
	1 5 10 15	
10	GTT GGA TGG TCA GAT TCA TAC ACC TGT GAA TAC CCT TTA AAC CTA AGG	94
	Val Gly Trp Ser Asp Ser Tyr Thr Cys Glu Tyr Pro Leu Asn Leu Arg	
	20 25 30	
15	GGA ACT AGG TTA AAA GAC GTT CAT CTC CAC GAA TTA TCT TGC AAC ACA	142
	Gly Thr Arg Leu Lys Asp Val His Leu His Glu Leu Ser Cys Asn Thr	
	35 40 45	
20	GCT CTG TTG ATT GTC ACC ATT GTG GTT ATT ATG CTA GTT CTG GGG TTG	190
	Ala Leu Leu Ile Val Thr Ile Val Val Ile Met Leu Val Leu Gly Leu	
	50 55 60	
25	GCT GTG GCC TTC TGC TGT CTC CAC TTT GAT CTG CCC TGG TAT CTC AGG	238
	Ala Val Ala Phe Cys Cys Leu His Phe Asp Leu Pro Trp Tyr Leu Arg	
	65 70 75	
30	ATG CTA GGT CAA TGC ACA CAA ACA TGG CAC AGG GTT AGG AAA ACA ACC	296
	Met Leu Gly Gln Cys Thr Gln Thr Trp His Arg Val Arg Lys Thr Thr	
	80 85 90 95	
35	CAA GAA CAA CTC AAG AGA AAT GTC CGA TTC CAC GCA TTT ATT TCA TAC	334
	Gln Glu Gln Leu Lys Arg Asn Val Arg Phe His Ala Phe Ile Ser Tyr	
	100 105 110	
40	AGT GAA CAT GAT TCT CTG TGG GTG AAG AAT GAA TTG ATC CCC AAT CTA	382
	Ser Glu His Asp Ser Leu Trp Val Lys Asn Glu Leu Ile Pro Asn Leu	
	115 120 125	
45	GAG AAG GAA GAT GGT TCT ATC TIG ATT TGC CTT TAT GAA AGC TAC TTT	430
	Glu Lys Glu Asp Gly Ser Ile Leu Ile Cys Leu Tyr Glu Ser Tyr Phe	
	130 135 140	
50	GAC CCT GGC AAA AGC ATT AGT GAA AAT ATT GTA AGC TTC ATT GAG AAA	478
	Asp Pro Gly Lys Ser Ile Ser Glu Asn Ile Val Ser Phe Ile Glu Lys	
	145 150 155	
55	AGC TAT AAG TCC ATC TTT GTT TTG TCT CCC AAC TTT GTC CAG AAT GAG	526
	Ser Tyr Lys Ser Ile Phe Val Leu Ser Pro Asn Phe Val Gln Asn Glu	
	160 165 170 175	
60	TGG TGC CAT TAT GAA TTC TAC TTT GCC CAC CAC AAT CTC TTC CAT GAA	574
	Trp Cys His Tyr Glu Phe Tyr Phe Ala His His Asn Leu Phe His Glu	
	180 185 190	
65	AAT TCT GAT CAC ATA ATT CTT ATC TTA CTG GAA CCC ATT CCA TTC TAT	622
	Asn Ser Asp His Ile Ile Leu Ile Leu Leu Glu Pro Ile Pro Phe Tyr	
	195 200 205	

	TGC ATT CCC ACC AGG TAT CAT AAA CTG GAA GCT CTC CTG GAA AAA AAA	670
	Cys Ile Pro Thr Arg Tyr His Lys Leu Glu Ala Leu Leu Glu Lys Lys	
	210 215 220	
5	GCA TAC TTG GAA TGG CCC AAG GAT AGG CGT AAA TGT GGG CTT TTC TGG	718
	Ala Tyr Leu Glu Trp Pro Lys Asp Arg Arg Lys Cys Gly Leu Phe Trp	
	225 230 235	
10	GCA AAC CTT CGA GCT GCT GTT AAT GTT AAT GTA TTA GCC ACC AGA GAA	766
	Ala Asn Leu Arg Ala Ala Val Asn Val Asn Val Leu Ala Thr Arg Glu	
	240 245 250 255	
15	ATG TAT GAA CTG CAG ACA TTC ACA GAG TTA AAT GAA GAG TCT CGA GGT	814
	Met Tyr Glu Leu Gln Thr Phe Thr Glu Leu Asn Glu Glu Ser Arg Gly	
	260 265 270	
20	TCT ACA ATC TCT CTG ATG AGA ACA GAC TGT CTA TAAATCCCA CAGTCCTTGG	867
	Ser Thr Ile Ser Leu Met Arg Thr Asp Cys Leu	
	275 280	
	GAAGTTGGGG ACCACATACA CTGTTGGGAT GTACATTGAT ACAACCTTTA TCATGGCAAT	927
25	TTGACAATAT TTATTAAT AAAAATGGT TATTCCTTC AAAAAAAAAA AAAAAAAAAA	987
	AAAAAAAAAA AA	999
30	SDAKIRHQAYSEVMMVGWSDSYTCEYPLNLRGTRLKDVHLHELSCNTALLIVTIVVIMLVGLAVAFCCCLHFDI WYLRMLGQCTQTWHRVRKTTQEQLKRNVRFAFISYSEHDSLWVKNELIPNLEKEDGSILICLYESYFDPGKS: ENIVSFIEKSYKSIFVLSPNFVQNEWCHYEYFAHHNLFHENS DHIILILEPIPFYCIPTRYHKEALLEKKK LEWPKDRRKCGLFWANLRAAVNVNVLATREMYELQTFTELNEESRGSTISLMRTDCL	
35	Further primate, e.g., human, DTLR8 (SEQ ID NO: 38 and 39):	
	gaatcatcca cgcacctgca gctctgctga gagagtgc aa gccgtggggg ttttgagctc 60	
	atcttcatca ttcatatgag gaaataagtg gtataatcct tggaaataca atg aga 116	
	Met Arg	
40	ctc atc aga aac att tac ata ttt tgt agt att gtt atg aca gca gag 164	
	Leu Ile Arg Asn Ile Tyr Ile Phe Cys Ser Ile Val Met Thr Ala Glu	
	-15 -10 -5	
45	ggt gat gct cca gag ctg cca gaa gaa agg gaa ctg atg acc aac tgc 212	
	Gly Asp Ala Pro Glu Leu Pro Glu Glu Arg Glu Leu Met Thr Asn Cys	
	-1 1 5 10 15	
50	tcc aac atg tct cta aga aag gtt ccc gca gac ttg acc cca gcc aca 260	
	Ser Asn Met Ser Leu Arg Lys Val Pro Ala Asp Leu Thr Pro Ala Thr	
	20 25 30	
55	aag aca ctg gat tta tcc tat aac ctc ctt ttt caa ctc cag agt tca 308	
	Thr Thr Leu Asp Leu Ser Tyr Asn Leu Leu Phe Gln Leu Gln Ser Ser	
	35 40 45	

		gat ttt cat tct gtc tcc aaa ctg aga gtt ttg att cta tgc cat aac	356
		Asp Phe His Ser Val Ser Lys Leu Arg Val Leu Ile Leu Cys His Asn	
		50 55 60	
5		aga att caa cag ctg gat ctc aaa acc ttt gaa ttc aac aag gag tta	404
		Arg Ile Gln Gln Leu Asp Leu Lys Thr Phe Glu Phe Asn Lys Glu Leu	
		65 70 75	
10		aga tat tta gat ttg tct aat aac aga ctg aag agt gta act tgg tat	452
		Arg Tyr Leu Asp Leu Ser Asn Asn Arg Leu Lys Ser Val Thr Trp Tyr	
		80 85 90 95	
15		tta ctg gca ggt ctc agg tat tta gat ctt tct ttt aat gac ttt gac	500
		Leu Leu Ala Gly Leu Arg Tyr Leu Asp Leu Ser Phe Asn Asp Phe Asp	
		100 105 110	
20		acc atg cct atc tgt gag gaa gct ggc aac atg tca cac ctg gaa atc	548
		Thr Met Pro Ile Cys Glu Glu Ala Gly Asn Met Ser His Leu Glu Ile	
		115 120 125	
25		cta ggt ttg agt ggg gca aaa ata caa aaa tca gat ttc cag aaa att	596
		Leu Gly Leu Ser Gly Ala Lys Ile Gln Lys Ser Asp Phe Gln Lys Ile	
		130 135 140	
30		gct cat ctg cat cta aat act gtc ttc tta gga ttc aga act ctt cct	644
		Ala His Leu His Leu Asn Thr Val Phe Leu Gly Phe Arg Thr Leu Pro	
		145 150 155	
35		cat tat gaa gaa ggt agc ctg ccc atc tta aac aca aca aaa ctg cac	692
		His Tyr Glu Glu Gly Ser Leu Pro Ile Leu Asn Thr Thr Lys Leu His	
		160 165 170 175	
40		att gtt tta cca atg gac aca aat ttc tgg gtt ctt ttg cgt gat gga	740
		Ile Val Leu Pro Met Asp Thr Asn Phe Trp Val Leu Leu Arg Asp Gly	
		180 185 190	
45		atc aag act tca aaa ata tta gaa atg aca aat ata gat ggc aaa agc	788
		Ile Lys Thr Ser Lys Ile Leu Glu Met Thr Asn Ile Asp Gly Lys Ser	
		195 200 205	
50		caa ttt gta agt tat gaa atg caa cga aat ctt agt tta gaa aat gct	836
		Gln Phe Val Ser Tyr Glu Met Gln Arg Asn Leu Ser Leu Glu Asn Ala	
		210 215 220	
55		aag aca tcg gtt cta ttg ctt aat aaa gtt gat tta ctc tgg gac gac	884
		Lys Thr Ser Val Leu Leu Leu Asn Lys Val Asp Leu Leu Trp Asp Asp	
		225 230 235	
60		ctt ttc ctt atc tta caa ttt gtt tgg cat aca tca gtg gaa cac ttt	932
		Leu Phe Leu Ile Leu Gln Phe Val Trp His Thr Ser Val Glu His Phe	
		240 245 250 255	
65		cag atc cga aat gcg act ttt ggt ggt aag gct tat ctt gac cac aat	980
		Gln Ile Arg Asn Val Thr Phe Gly Gly Lys Ala Tyr Leu Asp His Asn	
		260 265 270	

	tca ttt gac tac tca aat act gta atg aga act ata aaa ttg gag cat	1028
	Ser Phe Asp Tyr Ser Asn Thr Val Met Arg Thr Ile Lys Leu Glu His	
	275 280 285	
5	gta cat ttc aga gtg ttt tac att caa cag gat,aaa atc tat ttg ctt	1076
	Val His Phe Arg Val Phe Tyr Ile Gln Gln Asp Lys Ile Tyr Leu Leu	
	290 295 300	
10	ttg acc aaa atg gac ata gaa aac ctg aca ata tca aat gca caa atg	1124
	Leu Thr Lys Met Asp Ile Glu Asn Leu Thr Ile Ser Asn Ala Gln Met	
	305 310 315	
15	cca cac atg ctt ttc ccg aat tat cct acg aaa ttc caa tat tta aat	1172
	Pro His Met Leu Phe Pro Asn Tyr Pro Thr Lys Phe Gln Tyr Leu Asn	
	320 325 330 335	
20	ttt gcc aat aat atc tta aca gac gag ttg ttt aaa aga act atc caa	1220
	Phe Ala Asn Asn Ile Leu Thr Asp Glu Leu Phe Lys Arg Thr Ile Gln	
	340 345 350	
25	ctg cct cac ttg aaa act ctc att ttg aat ggc aat aaa ctg gag aca	1268
	Leu Pro His Leu Lys Thr Leu Ile Leu Asn Gly Asn Lys Leu Glu Thr	
	355 360 365	
30	ctt tct tta gta agt tgc ttt gct aac aac aca ccc ttg gaa cac ttg	1316
	Leu Ser Leu Val Ser Cys Phe Ala Asn Asn Thr Pro Leu Glu His Leu	
	370 375 380	
35	gat ctg agt caa aat cta tta caa cat aaa aat gat gaa aat tgc tca	1364
	Asp Leu Ser Gln Asn Leu Leu Gln His Lys Asn Asp Glu Asn Cys Ser	
	385 390 395	
40	tgg cca gaa act gtg gtc aat atg aat ctg tca tac aat aaa ttg tct	1412
	Trp Pro Glu Thr Val Val Asn Met Asn Leu Ser Tyr Asn Lys Leu Ser	
	400 405 410 415	
45	gat tct gtc ttc agg tgc ttg ccc aaa agt att caa ata ctt gac cta	1460
	Asp Ser Val Phe Arg Cys Leu Pro Lys Ser Ile Gln Ile Leu Asp Leu	
	420 425 430	
50	aat aat aac caa atc caa act gta cct aaa gag act att cat ctg atg	1508
	Asn Asn Asn Gln Ile Gln Thr Val Pro Lys Glu Thr Ile His Leu Met	
	435 440 445	
55	gcc tta cga gaa cta aat att gca ttt aat ttt cta act gat ctc cct	1556
	Ala Leu Arg Glu Leu Asn Ile Ala Phe Asn Phe Leu Thr Asp Leu Pro	
	450 455 460	
60	gga tgc agt cat ttc agt aga ctt tca gtt ctg aac att gaa atg aac	1604
	Gly Cys Ser His Phe Ser Arg Leu Ser Val Leu Asn Ile Glu Met Asn	
	465 470 475	
65	ttc att ctc agc cca tct ctg gat ttt gtt cag agc tgc cag gaa gtt	1652
	Phe Ile Leu Ser Pro Ser Leu Asp Phe Val Gln Ser Cys Gln Glu Val	
	480 485 490 495	

	aaa act cta aat gcg gga aga aat cca ttc cgg tgt acc tgt gaa tta	1700
	Lys Thr Leu Asn Ala Gly Arg Asn Pro Phe Arg Cys Thr Cys Glu Leu	
	500 505 510	
5	aaa aat ttc att cag ctt gaa aca tat tca gag gtc atg atg gtt gga	1748
	Lys Asn Phe Ile Gln Leu Glu Thr Tyr Ser Glu Val Met Met Val Gly	
	515 520 525	
10	tgg tca gat tca tao acc tgt gaa tac cct tta aac cta agg gga act	1796
	Trp Ser Asp Ser Tyr Thr Cys Glu Tyr Pro Leu Asn Leu Arg Gly Thr	
	530 535 540	
15	agg tta aaa gac gtt cat ctc cac gaa tta tct tgc aac aca gct ctg	1844
	Arg Leu Lys Asp Val His Leu His Glu Leu Ser Cys Asn Thr Ala Leu	
	545 550 555	
20	ttg att gtc acc att gtg gtt att atg cta gtt ctg ggg ttg gct gtg	1892
	Leu Ile Val Thr Ile Val Val Ile Met Leu Val Leu Gly Leu Ala Val	
	560 565 570 575	
25	gcc ttc tgc tgt ctc cac ttt gat ctg ccc tgg tat ctc agg atg cta	1940
	Ala Phe Cys Cys Leu His Phe Asp Leu Pro Trp Tyr Leu Arg Met Leu	
	580 585 590	
30	ggt caa tgc aca caa aca tgg cac agg gtt agg aaa aca acc caa gaa	1988
	Gly Gln Cys Thr Gln Thr Trp His Arg Val Arg Lys Thr Thr Gln Glu	
	595 600 605	
35	caa ctc aag aga aat gtc cga ttc cac gca ttt att tca tac agt gaa	2036
	Gln Leu Lys Arg Asn Val Arg Phe His Ala Phe Ile Ser Tyr Ser Glu	
	610 615 620	
40	cat gat tct ctg tgg gtg aag aat gaa ttg atc ccc aat cta gag aag	2084
	His Asp Ser Leu Trp Val Lys Asn Glu Leu Ile Pro Asn Leu Glu Lys	
	625 630 635	
45	gaa gat ggt tct atc ttg att tgc ctt tat gaa agc tac ttt gac cct	2132
	Glu Asp Gly Ser Ile Leu Ile Cys Leu Tyr Glu Ser Tyr Phe Asp Pro	
	640 645 650 655	
50	ggc aaa agc att agt gaa aat att gta agc ttc att gag aaa agc tat	2180
	Gly Lys Ser Ile Ser Glu Asn Ile Val Ser Phe Ile Glu Lys Ser Tyr	
	660 665 670	
55	aag tcc atc ttt gtt ttg tct ccc aac ttt gtc cag aat gag tgg tgc	2228
	Lys Ser Ile Phe Val Leu Ser Pro Asn Phe Val Gln Asn Glu Trp Cys	
	675 680 685	
60	cat tat gaa ttc tac ttt gcc cac cac aat ctc ttc cat gaa aat tct	2276
	His Tyr Glu Phe Tyr Phe Ala His His Asn Leu Phe His Glu Asn Ser	
	690 695 700	
65	gat cat ata att ctt atc tta ctg gaa ccc att cca ttc tat tgc att	2324
	Asp His Ile Ile Leu Ile Leu Leu Glu Pro Ile Pro Phe Tyr Cys Ile	
	705 710 715	

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ccc acc agg tat cat aaa ctg aaa gct ctc ctg gaa aaa aaa gca' tac 2372
Pro Thr Arg Tyr His Lys Leu Lys Ala Leu Leu Glu Lys Lys Ala Tyr
720 725 730 735

5 ttg gaa tgg ccc aag gat agg cgt aaa tgt ggg ctt ttc tgg gca aac 2420
Leu Glu Trp Pro Lys Asp Arg Arg Lys Cys Gly Leu Phe Trp Ala Asn
740 745 750

10 ctt cga gct gct att aat gtt aat gta tta gcc acc aga gaa atg tat 2468
Leu Arg Ala Ala Ile Asn Val Asn Val Leu Ala Thr Arg Glu Met Tyr
755 760 765

15 gaa ctg cag aca ttc aca gag tta aat gaa gag tct cga ggt tct aca 2516
Glu Leu Gln Thr Phe Thr Glu Leu Asn Glu Glu Ser Arg Gly Ser Thr
770 775 780

atc tct ctg atg aga aca gat tgt cta taaaatccca cagtccttgg 2563
Ile Ser Leu Met Arg Thr Asp Cys Leu
785 790

20 gaagttgggg accacatata ctgttgggat gtacattgat acaaccttta tgatggcaat 2623

ttgacaatat ttattaaat aaaaaatggt tattcccttc atatcagttt ctagaaggat 2683

25 ttctaagaat gtatcctata gaaacacctt cacaagtta taagggttta tggaaaaagg 2743

tggtcatccc aggattgttt ataatcatga aaaatgtggc caggtgcagt ggctcactct 2803

tgtaatccca gcactatggg aggccaagggt gggtgaccca cgaggtcaag agatggagac 2863

30 catcctggcc aacatggtga aacctgtct ctactaaaaa taaaaaatt agctgggct 2923

gatggtgcac gcctgtagtc ccagctactt gggaggctga ggcaggagaa tcgcttgaac 2983

35 ccgggagctg gcagttgcag tgagctgaga tcgagccact gcactccagc ctggtgacag 3043

agc 3046

40 MRLIRNIYIFCSI VMTAEGDAPELPEERELMTNCSNM SLRKVPADLTPATTTLDLSYNLLFQLQSSDFH
SVSKLRVLILCHNRIQQDLKTFEFNKELRYLDLSNNRLKSVTWYLLAGLRYLDLSFNDFDTMPICEEA
GNMSHLEILGLSGAKIQKSDFQKIAHLHLNTVFLGFRTPHYEEGSLPILNTTKLHIVLPMDTNFWVLL
RDGIKTSKILEMTNIDGKSQFVS YEMQRNLSLENAKTSVLLLNKVDLLWDDLFLILQFVWHTSVEHFQI
RNVTFGCKAYLDHNSFDYSNTVMRTIKLEHVHFRVFYIQQDKIYLLLT KMDIENLTISNAQMPHMLFPN
YPTKFQYLNFAANNILTDELFKRTIQLPHLKTILNNGNRLETLSLVSCFANNTPLEHLDLSQNLLOHKND

45 ENC SWPETVVMNLSYNKLSDSVFRCLPKSIQILDNNNQIQTVPKETIHLMALRELNIAFNFLTDLPG
CSHF SRLSVLNIEMNFILSPSLDFVQSCQEVKTLNAGRNPFRCTCELKNFIQLETYSEVMVGVGSDSYT
CEYPLNLRGTRLKDVHLHELSCNTALLIVTIVVIMLVGLAVAFCLHFDLPWYLRMLGQCTQTWHRVR
KTTQEQ LKRNVRFHAFISYSEHDSLWVKNELIPNLEKEDGSILICLYESYFDPGKSISENIVSFIKSY
KSIFVLSPNFVQNEWCHYEYFPAHNNLFHENS DHIIILILEPIPFYCIPTRYHXLKALLEKKAYLEWPK

50 DRRKCGLFWANLRAAINVNVLATREMYELQTFTELNEESRGSTISLMRTDCL

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Table 9: Partial nucleotide and amino acid sequences (see SEQ ID NO: 21 and 22) of a mammalian, e.g., primate, human, DNAX Toll like Receptor 9 (DTLR9).

5	AAG AAC TCC AAA GAA AAC CTC CAG TTT CAT GCT TTT ATT TCA TAT AGT	48
	Lys Asn Ser Lys Glu Asn Leu Gln Phe His Ala Phe Ile Ser Tyr Ser	
	1 5 10 15	
10	GAA CAT GAT TCT GCC TGG GTG AAA AGT GAA TTG GTA CCT TAC CTA GAA	96
	Glu His Asp Ser Ala Trp Val Lys Ser Glu Leu Val Pro Tyr Leu Glu	
	20 25 30	
15	AAA GAA GAT ATA CAG ATT TGT CTT CAT GAG AGA AAC TTT GTC CCT GGC	144
	Lys Glu Asp Ile Gln Ile Cys Leu His Glu Arg Asn Phe Val Pro Gly	
	35 40 45	
20	AAG AGC ATT GTG GAA AAT ATC ATC AAC TGC ATT GAG AAG AGT TAC AAG	192
	Lys Ser Ile Val Glu Asn Ile Ile Asn Cys Ile Glu Lys Ser Tyr Lys	
	50 55 60	
25	TCC ATC TTT GTT TTG TCT CCC AAC TTT GTC CAG AGT GAG TGG TGC CAT	240
	Ser Ile Phe Val Leu Ser Pro Asn Phe Val Gln Ser Glu Trp Cys His	
	65 70 75 80	
30	TAC GAA CTC TAT TTT GCC CAT CAC AAT CTC TTT CAT GAA GGA TCT AAT	288
	Tyr Glu Leu Tyr Phe Ala His His Asn Leu Phe His Glu Gly Ser Asn	
	85 90 95	
35	AAC TTA ATC CTC ATC TTA CTG GAA CCC ATT CCA CAG AAC AGC ATT CCC	336
	Asn Leu Ile Leu Ile Leu Leu Glu Pro Ile Pro Gln Asn Ser Ile Pro	
	100 105 110	
40	AAC AAG TAC CAC AAG CTG AAG GCT CTC ATG ACG CAG CGG ACT TAT TTG	384
	Asn Lys Tyr His Lys Leu Lys Ala Leu Met Thr Gln Arg Thr Tyr Leu	
	115 120 125	
45	CAG TGG CCC AAG GAG AAA AGC AAA CGT GGG CTC TTT TGG GCT	426
	Gln Trp Pro Lys Glu Lys Ser Lys Arg Gly Leu Phe Trp Ala	
	130 135 140	
50	A	427
	KNSKENLQFHAFISYSEHDSAWVKSELVPYLEKEDIQICLHERNFVPGKSIVENIINCIEKSYKSIFVLSPNE	
	SEWCHYELYFAHHNLFHEGSNNLILILLEPIPNQNSIPNKYHKLKALMTQRTYLQWPKEKSKRGLFWA	

Further primate, e.g., human DTLR9 (SEQ ID NO: 40 and 41):

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aagaatttgg actcatatca agatgctctg aagaagaaca acccttttagg atagccactg 60
5  caacatc atg acc aaa gac aaa gaa cct att gtt aaa agc ttc cat ttt 109
    Met Thr Lys Asp Lys Glu Pro Ile Val Lys Ser Phe His Phe
    -30 -25 -20
10  gtt tgc ctt atg atc ata ata gtt gga acc aga atc cag ttc tcc gac 157
    Val Cys Leu Met Ile Ile Ile Val Gly Thr Arg Ile Gln Phe Ser Asp
    -15 -10 -5
15  gga aat gaa ttt gca gta gac aag tca aaa aga ggt ctt att cat gtt 205
    Gly Asn Glu Phe Ala Val Asp Lys Ser Lys Arg Gly Leu Ile His Val
    -1 1 5 10 15
20  cca aaa gac cta ccg ctg aaa acc aaa gtc tta gat atg tct cag aac 253
    Pro Lys Asp Leu Pro Leu Lys Thr Lys Val Leu Asp Met Ser Gln Asn
    20 25 30
25  tac atc gct gag ctt cag gtc tct gac atg agc ttt cta tca gag ttg 301
    Tyr Ile Ala Glu Leu Gln Val Ser Asp Met Ser Phe Leu Ser Glu Leu
    35 40 45
30  aca gtt ttg aga ctt tcc cat aac aga atc cag cta ctt gat tta agt 349
    Thr Val Leu Arg Leu Ser His Asn Arg Ile Gln Leu Leu Asp Leu Ser
    50 55 60
35  gtt ttc aag ttc aac cag gat tta gaa tat ttg gat tta tct cat aat 397
    Val Phe Lys Phe Asn Gln Asp Leu Glu Tyr Leu Asp Leu Ser His Asn
    65 70 75
40  cag ttg caa aag ata tcc tgc cat cct att gtg agt ttc agg cat tta 445
    Gln Leu Gln Lys Ile Ser Cys His Pro Ile Val Ser Phe Arg His Leu
    80 85 90 95
45  gat ctc tca ttc aat gat ttc aag gcc ctg ccc atc tgt aag gaa ttt 493
    Asp Leu Ser Phe Asn Asp Phe Lys Ala Leu Pro Ile Cys Lys Glu Phe
    100 105 110
50  ggc aac tta tca caa ctg aat ttc ttg gga ttg agt gct atg aag ctg 541
    Gly Asn Leu Ser Gln Leu Asn Phe Leu Gly Leu Ser Ala Met Lys Leu
    115 120 125
55  caa aaa tta gat ttg ctg cca att gct cac ttg cat cta agt tat atc 589
    Gln Lys Leu Asp Leu Leu Pro Ile Ala His Leu His Leu Ser Tyr Ile
    130 135 140
60  ctt ctg gat tta aga aat tat tat ata aaa gaa aat gag aca gaa agt 637
    Leu Leu Asp Leu Arg Asn Tyr Tyr Ile Lys Glu Asn Glu Thr Glu Ser
    145 150 155
65  cta caa att ctg aat gca aaa acc ctt cac ctt gtt ttt cac cca act 685
    Leu Gln Ile Leu Asn Ala Lys Thr Leu His Leu Val Phe His Pro Thr
    160 165 170 175

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	agt tta ttc gct atc caa gtg aac ata tca gtt aat acc tta ggg tgc	733
	Ser Leu Phe Ala Ile Gln Val Asn Ile Ser Val Asn Thr Leu Gly Cys	
	180 185 190	
5	tta caa ctg act aat att aaa ttg aat gat gac aac tgt caa gtt ttc	781
	Leu Gln Leu Thr Asn Ile Lys Leu Asn Asp Asp Asn Cys Gln Val Phe	
	195 200 205	
10	att aaa ttt tta tca gaa ctc acc aga ggt cca acc tta ctg aat ttt	829
	Ile Lys Phe Leu Ser Glu Leu Thr Arg Gly Pro Thr Leu Leu Asn Phe	
	210 215 220	
15	acc ctc aac cac ata gaa acg act tgg aaa tgc ctg gtc aga gtc ttt	877
	Thr Leu Asn His Ile Glu Thr Thr Trp Lys Cys Leu Val Arg Val Phe	
	225 230 235	
20	caa ttt ctt tgg ccc aaa cct gtg gaa tat ctc aat att tac aat tta	925
	Gln Phe Leu Trp Pro Lys Pro Val Glu Tyr Leu Asn Ile Tyr Asn Leu	
	240 245 250 255	
25	aca ata att gaa agc att cgt gaa gaa gat ttt acc tat tct aaa acg	973
	Thr Ile Ile Glu Ser Ile Arg Glu Glu Asp Phe Thr Tyr Ser Lys Thr	
	260 265 270	
30	aca ttg aaa gca ttg aca ata gaa cat atc acg aac caa gtt ttt ctg	1021
	Thr Leu Lys Ala Leu Thr Ile Glu His Ile Thr Asn Gln Val Phe Leu	
	275 280 285	
35	ttt tca cag aca gct ttg tac acc gtg ttt tct gag atg aac att atg	1069
	Phe Ser Gln Thr Ala Leu Tyr Thr Val Phe Ser Glu Met Asn Ile Met	
	290 295 300	
40	atg tta acc att tca gat aca cct ttt ata cac atg ctg tgt cct cat	1117
	Met Leu Thr Ile Ser Asp Thr Pro Phe Ile His Met Leu Cys Pro His	
	305 310 315	
45	gca cca agc aca ttc aag ttt ttg aac ttt acc cag aac gtt ttc aca	1165
	Ala Pro Ser Thr Phe Lys Phe Leu Asn Phe Thr Gln Asn Val Phe Thr	
	320 325 330 335	
50	gat agt att ttt gaa aaa tgt tcc acg tta gtt aaa ttg gag aca ctt	1213
	Asp Ser Ile Phe Glu Lys Cys Ser Thr Leu Val Lys Leu Glu Thr Leu	
	340 345 350	
55	atc tta caa aag aat gga tta aaa gac ctt ttc aaa gta ggt ctc atg	1261
	Ile Leu Gln Lys Asn Gly Leu Lys Asp Leu Phe Lys Val Gly Leu Met	
	355 360 365	
60	acg aag gat atg cct tct ttg gaa ata ctg gat gtt agc tgg aat tct	1309
	Thr Lys Asp Met Pro Ser Leu Glu Ile Leu Asp Val Ser Trp Asn Ser	
	370 375 380	
65	ttg gaa tct ggt aga cat aaa gaa aac tgc act tgg gtt gag agt ata	1357
	Leu Glu Ser Gly Arg His Lys Glu Asn Cys Thr Trp Val Glu Ser Ile	
	385 390 395	

	gtg gtg tta aat ttg tct tca aat atg ctt act gac tct gtt ttc aga	1405
	Val Val Leu Asn Leu Ser Ser Asn Met Leu Thr Asp Ser Val Phe Arg	
	400 405 410 415	
5	tgt tta cct ccc agg atc aag gta ctt gat ctt cac agc aat aaa ata	1453
	Cys Leu Pro Pro Arg Ile Lys Val Leu Asp Leu His Ser Asn Lys Ile	
	420 425 430	
10	aag agc gtt cct aaa'caa gtc gta aaa ctg gaa gct ttg caa gaa ctc	1501
	Lys Ser Val Pro Lys Gln Val Val Lys Leu Glu Ala Leu Gln Glu Leu	
	435 440 445	
15	aat gtt gct ttc aat tct tta act gac ctt cct gga tgt ggc agc ttt	1549
	Asn Val Ala Phe Asn Ser Leu Thr Asp Leu Pro Gly Cys Gly Ser Phe	
	450 455 460	
20	agc agc ctt tct gta ttg atc att gat cac aat tca gtt tcc cac cca	1597
	Ser Ser Leu Ser Val Leu Ile Ile Asp His Asn Ser Val Ser His Pro	
	465 470 475	
25	tcg gct gat ttc ttc cag agc tgc cag aag atg agg tca ata aaa gca	1645
	Ser Ala Asp Phe Phe Gln Ser Cys Gln Lys Met Arg Ser Ile Lys Ala	
	480 485 490 495	
30	ggg gac aat cca ttc caa tgt acc tgt gag cta aga gaa ttt gtc aaa	1693
	Gly Asp Asn Pro Phe Gln Cys Thr Cys Glu Leu Arg Glu Phe Val Lys	
	500 505 510	
35	aat ata gac caa gta tca agt gaa ctg tta gag ggc tgg cct gat tct	1741
	Asn Ile Asp Gln Val Ser Ser Glu Val Leu Glu Gly Trp Pro Asp Ser	
	515 520 525	
40	tat aag tgt gac tac cca gaa agt tat aga gga agc cca cta aag gac	1789
	Tyr Lys Cys Asp Tyr Pro Glu Ser Tyr Arg Gly Ser Pro Leu Lys Asp	
	530 535 540	
45	ttt cac atg tct gaa tta tcc tgc aac ata act ctg ctg atc gtc acc	1837
	Phe His Met Ser Glu Leu Ser Cys Asn Ile Thr Leu Leu Ile Val Thr	
	545 550 555	
50	atc ggt gcc acc atg ctg gtg ttg gct gtg act gtg acc tcc ctc tgc	1885
	Ile Gly Ala Thr Met Leu Val Leu Ala Val Thr Val Thr Ser Leu Cys	
	560 565 570 575	
55	atc tac ttg gat ctg ccc tgg tat ctc agg atg gtg tgc cag tgg acc	1933
	Ile Tyr Leu Asp Leu Pro Trp Tyr Leu Arg Met Val Cys Gln Trp Thr	
	580 585 590	
60	cag act cgg cgc agg gcc agg aac ata ccc tta gaa gaa ctc caa aga	1981
	Gln Thr Arg Arg Arg Ala Arg Asn Ile Pro Leu Glu Glu Leu Gln Arg	
	595 600 605	
65	aac ctc cag ttt cat gct ttt att tca tat agt gaa cat gat tct gcc	2029
	Asn Leu Gln Phe His Ala Phe Ile Ser Tyr Ser Glu His Asp Ser Ala	
	610 615 620	

2077
 tgg gtg aaa agt gaa ttg gta cct tac cta gaa aaa gaa gat ata cag
 Trp Val Lys Ser Glu Leu Val Pro Tyr Leu Glu Lys Glu Asp Ile Gln
 625 630 635

5 att tgt ctt cat gag agg aac ttt gtc cct ggc aag agc att gtg gaa 2125
 Ile Cys Leu His Glu Arg Asn Phe Val Pro Gly Lys Ser Ile Val Glu
 640 645 650

10 aat atc atc aac tgc att gag aag agt tac aag tcc atc ttt gtt ttg 2173
 Asn Ile Ile Asn Cys Ile Glu Lys Ser Tyr Lys Ser Ile Phe Val Leu
 660 665 670

15 tct ccc aac ttt gtc cag agt gag tgg tgc cat tac gaa ctc tat ttt 2221
 Ser Pro Asn Phe Val Gln Ser Glu Trp Cys His Tyr Glu Leu Tyr Phe
 675 680 685

20 gcc cat cac aat ctc ttt cat gaa gga tct aat aac tta atc ctc atc 2269
 Ala His His Asn Leu Phe His Glu Gly Ser Asn Asn Leu Ile Leu Ile
 690 695 700

tta ctg gaa ccc att cca cag aac agc att ccc aac aag tac cac aag 2317
 Leu Leu Glu Pro Ile Pro Gln Asn Ser Ile Pro Asn Lys Tyr His Lys
 705 710 715

25 ctg aag gct ctc atg acg cag cgg act tat ttg cag tgg ccc aag gag 2365
 Leu Lys Ala Leu Met Thr Gln Arg Thr Tyr Leu Gln Trp Pro Lys Glu
 720 725 730

30 aaa agc aaa cgt ggg ctc ttt tgg gct aac att aga gcc gct ttt aat 2413
 Lys Ser Lys Arg Gly Leu Phe Trp Ala Asn Ile Arg Ala Ala Phe Asn
 740 745 750

35 atg aaa tta aca cta gtc act gaa aac aat gat gtg aaa tct 2455
 Met Lys Leu Thr Leu Val Thr Glu Asn Asn Asp Val Lys Ser
 755 760 765

taaaaaaatt taggaaattc aacttaagaa accattattt acttggatga tggatgaatag 2515

40 tacagtcgta agtnactgtc tggagggtgcc tccattatcc tcatgccttc aggaaagact 2575

taacaaaaaac aatgtttcat ctgggggaact gagctaggcg gtgagggttag cctgccagtt 2635

agagacagcc cagtctcttc tggtttaate attatgtttc aaattgaaac agtctctttt 2695

45 gagtaaatgc tcagtttttc agctcctctc cactctgctt tcccaaatgg attctgttgg 2755

tgaag 2760

MTKDKEPIVKS FHFVCLMIIIVGTRI QPSDGNFÀVDKSKRGLIHVPKDLPLKTKVLDMSONYIAELQV
SDMSFLSELT VLR LSHNRIQLDLSVFKFNQDLEYLDLSHNQLQKISCHPIVSFRHLDLSFNDFKALPI
CKEFGNLSQLN FLGLS AMKLQXLDLLPIAHLHLSYILLDLRNYIYIKENETESLQILNAKTLHLV FHPTS
5 LFAIQVNISVNTLGCLQLTNIKLNDDNCQVFIKFLSELTRGPTLLNFTLNHIETTWKCLVRVFQFLWPK
PVEYLNINLTIIIESIREEDFTYSKTKALKALTIEHITNQVFLFSQTALYTVFSEMNIIMMLTISDTPFFIH
MLCPHAPSTFKFLNFTQNVFTDSIFEKCS TLVKLET LILQKNGLKDLFKVGLMTKDMPSLEILDVSWNS
LESGRHKENCTWVESIVVLNLSSNMLTDSVFRCLPPRIKVLDLHSNKIKSVPKQVVKLEALQELNVAFN
SLTDLP GCGSFSSLSVLIIDHNSVSHPSADFFQSCQKMRSIKAGDNPFQCTCELREFVKNIDQVSSEVL
10 EGWPD SYKCDYPESYRGSPLKDFHMSSELSCNITLLIVTIGATMLVLAVTVTSLCIYLDLPWYLRMVCQW
TQTRRRARNIPLEELQRNLQFHAFISYSEHDSAWVKSELVPYLEKEDIQICLHERNFVPGKSIVENIIN
CIEKSYKSIFVLSPNFVQSEWCHYELYFAHNNLFHEGSNNLILILLEPIPQNSIPNKYHKLKALMTQRT
YLQWPKEKSKRGLFWANIRAAFNMKLT LV TENNDVKS

Table 10: Nucleotide and amino acid sequences (see SEQ ID NO: 23 and 24) of a mammalian, e.g., primate, human, DNAX Toll like Receptor 10 (DILRIC). Nucleotides 54, 103, and 345 are designated A; each may be A or G; nucleotide 313 designated G, may be G or T; and nucleotides 316, 380, 407, and 408 designated C; each may be A, C, G, or T.

5	GCT TCC ACC TGT GCC TGG CCT GGC TTC CCT GGC GGG GGC GGC AAA GTG	48
	Ala Ser Thr Cys Ala Trp Pro Gly Phe Pro Gly Gly Gly Gly Lys Val	
	1 5 10 15	
10	GGC GAA ATG AGG ATG CCC TGC CCT ACG ATG CCT TCG TGG TCT TCG ACA	96
	Gly Glu Met Arg Met Pro Cys Pro Thr Met Pro Ser Trp Ser Ser Thr	
	20 25 30	
15	AAA CGC AGA GCG CAG TGG CAG ACT GGG TGT ACA ACG AGC TTC GGG GGC	144
	Lys Arg Arg Ala Gln Trp Gln Thr Gly Cys Thr Thr Ser Phe Gly Gly	
	35 40 45	
20	AGC TGG AGG AGT GCC GTG GGC GCT GGG CAC TCC GCC TGT GCC TGG AGG	192
	Ser Trp Arg Ser Ala Val Gly Ala Gly His Ser Ala Cys Ala Trp Arg	
	50 55 60	
25	AAC GCG ACT GGC TGC CTG GCA AAA CCC TCT TTG AGA ACC TGT GGG CCT	240
	Asn Ala Thr Gly Cys Leu Ala Lys Pro Ser Leu Arg Thr Cys Gly Pro	
	65 70 75 80	
30	CGG TCT ATG GCA GCC GCA AGA CGC TGT TTG TGC TGG CCC ACA CGG ACC	288
	Arg Ser Met Ala Ala Ala Arg Arg Cys Leu Cys Trp Pro Thr Arg Thr	
	85 90 95	
35	GGG TCA GTG GTC TCT TGC GCG CCA GTT CTC CTG CTG GCC CAG CAG CGC	336
	Gly Ser Val Val Ser Cys Ala Pro Val Leu Leu Leu Ala Gln Gln Arg	
	100 105 110	
40	CTG CTG GAA GAC CGC AAG GAC GTC GTG GTG CTG GTG ATC CTA ACG CCT	384
	Leu Leu Glu Asp Arg Lys Asp Val Val Val Leu Val Ile Leu Thr Pro	
	115 120 125	
45	GAC GGC CAA GCC TCC CGA CTA CCC GAT GCG CTG ACC AGC GCC TCT GCC	432
	Asp Gly Gln Ala Ser Arg Leu Pro Asp Ala Leu Thr Ser Ala Ser Ala	
	130 135 140	
50	GCC AGA GTG TCC TCC TCT GGC CCC ACC AGC CCA GTG GTC GCG CAG CTT	480
	Ala Arg Val Ser Ser Ser Gly Pro Thr Ser Pro Val Val Ala Gln Leu	
	145 150 155 160	
55	CTG ASG CCA GCA TGC ATG GCC CTG ACC AGG GAC AAC CAC CAC TTC TAT	528
	Leu Arg Pro Ala Cys Met Ala Leu Thr Arg Asp Asn His His Phe Tyr	
	165 170 175	
60	AAC CGG AAC TTC TGC CAG GGA ACC CAC GGC CGA ATA GCC GTG AGC CGG	576
	Asn Arg Asn Phe Cys Gln Gly Thr His Gly Arg Ile Ala Val Ser Arg	
	180 185 190	

	AAT CCT GCA CGG TGC CAC CTC CAC ACA CAC CTA ACA TAT GCC TGC CTG	624
	Asn Pro Ala Arg Cys His Leu His Thr His Leu Thr Tyr Ala Cys Leu	
	195 200 205	
5	ATC TGACCAACAC ATGCTCGCCA CCCTCACCAC ACACC	662
	Ile	
10	ASTCANPGEFEGGGKVGEMRMPCPTMPSWSSTKRRAQWQTGCTTSFGGSNRSVAVGAGHSACAWRNATGCLAKPSL RTCGPRSMAPARRCLCNPTRTGSSVSCAPVLLLAQQRLLLEDKDVVVLVILTFDGOASRLPDALTSASAARVSSS GPTSPVVAQLLRACMALTRDNHHFYNNRNFQSTHGRIAVSRNPARCHLHTLTYACLI	
15	additional primate, e.g., human DTLR10 sequence (SEQ ID NO: 33 and 34); nucleotide 854 designated A, may be A or T; and nucleotides 1171 and 1172 designated C, each may be A, C, G, or T:	
	CTG CCT GCT GGC ACC CGG CTC CGG AGG CTG GAT GTC AGC TGC AAC AGC	48
	Leu Pro Ala Gly Thr Arg Leu Arg Arg Leu Asp Val Ser Cys Asn Ser	
	1 5 10 15	
20	ATC AGC TTC GTG GCC CCC GGC TTC TTT TCC AAG GCC AAG GAG CTG CGA	96
	Ile Ser Phe Val Ala Pro Gly Phe Phe Ser Lys Ala Lys Glu Leu Arg	
	20 25 30	
25	GAG CTC AAC CTT AGC GCC AAC GCC CTC AAG ACA GTG GAC CAC TCC TGG	144
	Glu Leu Asn Leu Ser Ala Asn Ala Leu Lys Thr Val Asp His Ser Trp	
	35 40 45	
30	TTT GGG CCC CTG GCG AGT GCC CTG CAA ATA CTA GAT GTA AGC GCC AAC	192
	Phe Gly Pro Leu Ala Ser Ala Leu Gln Ile Leu Asp Val Ser Ala Asn	
	50 55 60	
35	CCT CTG CAC TGC GCC TGT GGG GCG GCC TTT ATG GAC TTC CTG CTG GAG	240
	Pro Leu His Cys Ala Cys Gly Ala Ala Phe Met Asp Phe Leu Leu Glu	
	65 70 75 80	
	GTG CAG GCT GCC GTC CCC GGT CTG CCC AGC CGG GTG AAG TGT GGC AGT	288
	Val Gln Ala Ala Val Pro Gly Leu Pro Ser Arg Val Lys Cys Gly Ser	
	85 90 95	
40	CCG GGC CAG CTC CAG GGC CTC AGC ATC TTT GCA CAG GAC CTG CGC CTC	336
	Pro Gly Gln Leu Gln Gly Leu Ser Ile Phe Ala Gln Asp Leu Arg Leu	
	100 105 110	
45	TGC CTG GAT GAG GCC CTC TCC TGG GAC TGT TTC GCC CTC TCG CTG CTG	384
	Cys Leu Asp Glu Ala Leu Ser Trp Asp Cys Phe Ala Leu Ser Leu Leu	
	115 120 125	
50	GCT GTG GCT CTG GGC CTG GGT GTC CCC ATG CTG CAT CAC CTC TGT GGC	432
	Ala Val Ala Leu Gly Leu Gly Val Pro Met Leu His His Leu Cys Gly	
	130 135 140	
55	TGG GAC CTC TGG TAC TGC TTC CAC CTG TGC CTG GCC TGG CTT CCC TGG	480
	Trp Asp Leu Trp Tyr Cys Phe His Leu Cys Leu Ala Trp Leu Pro Trp	
	145 150 155 160	

	CGG GGG CGG CAA AGT GGG CGA GAT GAG GAT GCC CTG CCC TAC GAT GCC	528
	Arg Gly Arg Gln Ser Gly Arg Asp Glu Asp Ala Leu Pro Tyr Asp Ala	
	165 170 175	
5	TTC GTG GTC TTC GAC AAA ACG CAG AGC GCA GTG GCA GAC TGG GTG TAC	576
	Phe Val Val Phe Asp Lys Thr Gln Ser Ala Val Ala Asp Trp Val Tyr	
	180 185 190	
10	AAC GAG CTT CGG GGG CAG CTG GAG GAG TGC CGT GGG CGC TGG GCA CTC	624
	Asn Glu Leu Arg Gly Gln Leu Glu Glu Cys Arg Gly Arg Trp Ala Leu	
	195 200 205	
15	CGC CTG TGC CTG GAG GAA CGC GAC TGG CTG CCT GGC AAA ACC CTC TTT	672
	Arg Leu Cys Leu Glu Glu Arg Asp Trp Leu Pro Gly Lys Thr Leu Phe	
	210 215 220	
20	GAG AAC CTG TGG GCC TCG GTC TAT GGC AGC CGC AAG ACG CTG TTT GTG	720
	Glu Asn Leu Trp Ala Ser Val Tyr Gly Ser Arg Lys Thr Leu Phe Val	
	225 230 235 240	
25	CTG GCC CAC ACG GAC CGG GTC AGT GGT CTC TTG CGC GCC AGC TTC CTG	768
	Leu Ala His Thr Asp Arg Val Ser Gly Leu Leu Arg Ala Ser Phe Leu	
	245 250 255	
30	CTG GCC CAG CAG CGC CTG CTG GAG GAC CGC AAG GAC GTC GTG GTG CTG	816
	Leu Ala Gln Gln Arg Leu Leu Glu Asp Arg Lys Asp Val Val Val Leu	
	260 265 270	
35	GTG ATC CTG AGC CCT GAC GGC CGC CGC TCC CGC TAC GAG CGG CTG CGC	864
	Val Ile Leu Ser Pro Asp Gly Arg Arg Ser Arg Tyr Glu Arg Leu Arg	
	275 280 285	
40	CAG CGC CTC TGC CGC CAG AGT GTC CTC CTC TGG CCC CAC CAG CCC AGT	912
	Gln Arg Leu Cys Arg Gln Ser Val Leu Leu Trp Pro His Gln Pro Ser	
	290 295 300	
45	GGT CAG CGC AGC TTC TGG GCC CAG CTG GGC ATG GCC CTG ACC AGG GAC	960
	Gly Gln Arg Ser Phe Trp Ala Gln Leu Gly Met Ala Leu Thr Arg Asp	
	305 310 315 320	
50	AAC CAC CAC TTC TAT AAC CGG AAC TTC TGC CAG GGA CCC ACG GCC GAA	1008
	Asn His His Phe Tyr Asn Arg Asn Phe Cys Gln Gly Pro Thr Ala Glu	
	325 330 335	
50	TAGCCGTGAG CCGGAATCCT GCACGGTGCC ACCTCCACAC TCACCTCACC TCTGCCTGCC	1068
	TGGTCTGACC CTCCCCTGCT CGCCTCCCTC ACCCCACACC TGACACAGAG CAGGCACTCA	1128
50	ATAAATGCTA CCGAAGGCTA AAAAAAAAAA AAAAAAAAAA AACCA	1173

LPAGTRLRLDLVSCNSISFVAPGFFSKAKELRELNLSANALKTVDSWFGPLASALQILDVSANPLHCACGAAFM
 DFLLEVQAAPVGLPSRVKCGSPGQLQGLSIFAQDLRLCLDEALSWDCFALSLLAVALGLGVPMHLHLGWDLMYC
 FHLCLAWLPWRGRQSGRDEDALPYDAFVVFDXTQSAVADWVYNELRGQLEECRGRWALRLCLEERDWLPGKTLPE
 NLWASVYGSRKTLFVLAHTDRVSGLLRASFLLAQORLLEDKDVVVLVILSPDGRRSRY.RLRQRLCRQSVLLWP
 5 HQPSGQRSPWAQLGMALTRDNEHFYNNFCQGPTAE

Further primate, e.g., human, DTLR10 (SEQ ID NO: 42 and 43):

10	atg ccc atg aag tgg agt ggg tgg agg tgg agc tgg ggg ccg gcc act	48
	Met Pro Met Lys Trp Ser Gly Trp Arg Trp Ser Trp Gly Pro Ala Thr	
	-45 -40 -35	
15	caa aca gcc ctc cca ccc cca cag ggt ttc tgc cgc agc gcc ctg cac	96
	His Thr Ala Leu Pro Pro Pro Gln Gly Phe Cys Arg Ser Ala Leu His	
	-30 -25 -20	
20	ccg ctg tct ctc ctg gtg cag gcc atc atg ctg gcc atg acc ctg gcc	144
	Pro Leu Ser Leu Leu Val Gln Ala Ile Met Leu Ala Met Thr Leu Ala	
	-15 -10 -5 -1	
25	ctg ggt acc ttg cct gcc ttc cta ccc tgt gag ctc cag ccc cac ggc	192
	Leu Gly Thr Leu Pro Ala Phe Leu Pro Cys Glu Leu Gln Pro His Gly	
	1 5 10 15	
30	ctg gtg aac tgc aac tgg ctg ttc ctg aag tct gtg ccc cac ttc tcc	240
	Leu Val Asn Cys Asn Trp Leu Phe Leu Lys Ser Val Pro His Phe Ser	
	20 25 30	
35	atg gca gca ccc cgt ggc aat gtc acc agc ctt tcc ttg tcc tcc aac	288
	Met Ala Ala Pro Arg Gly Asn Val Thr Ser Leu Ser Leu Ser Ser Asn	
	35 40 45	
40	cgc atc cac cac ctc cat gat tct gac ttt gcc cac ctg ccc agc ctg	336
	Arg Ile His His Leu His Asp Ser Asp Phe Ala His Leu Pro Ser Leu	
	50 55 60	
45	cgg cat ctc aac ctc aag tgg aac tgc ccg ccg gtt ggc ctc agc ccc	384
	Arg His Leu Asn Leu Lys Trp Asn Cys Pro Pro Val Gly Leu Ser Pro	
	65 70 75 80	
50	atg cac ttc ccc tgc cac atg acc atc gag ccc agc acc ttc ttg gct	432
	Met His Phe Pro Cys His Met Thr Ile Glu Pro Ser Thr Phe Leu Ala	
	85 90 95	
55	gtg ccc acc ctg gaa gag cta aac ctg agc tac aac aac atc atg act	480
	Val Pro Thr Leu Glu Glu Leu Asn Leu Ser Tyr Asn Asn Ile Met Thr	
	100 105 110	
60	gtg cct gcg ctg ccc aaa tcc ctc ata tcc ctg tcc ctc agc cat acc	528
	Val Pro Ala Leu Pro Lys Ser Leu Ile Ser Leu Ser Leu Ser His Thr	
	115 120 125	
65	aac atc ctg atg cta gac tct gcc agc ctc gcc ggc ctg cat gcc ctg	576
	Asn Ile Leu Met Leu Asp Ser Ala Ser Leu Ala Gly Leu His Ala Leu	
	130 135 140	

	cgc ttc cta ttc atg gac ggc aac tgt tat tac aag aac ccc tgc agg	624
	Arg Phe Leu Phe Met Asp Gly Asn Cys Tyr Tyr Lys Asn Pro Cys Arg	
	145 150 155 160	
5	cag gca ctg gag gtg gcc cgg ggt gcc ctc ctt ggc ctg ggc aac ctc	672
	Gln Ala Leu Glu Val Ala Pro Gly Ala Leu Leu Gly Leu Gly Asn Leu	
	165 170 175	
10	acc cac ctg tca ctc aag tac aac aac ctc act gtg gtg ccc cgc aac	720
	Thr His Leu Ser Leu Lys Tyr Asn Asn Leu Thr Val Val Pro Arg Asn	
	180 185 190	
15	ctg cct tcc agc ctg gag tat ctg ctg ttg tcc tac aac cgc atc gtc	768
	Leu Pro Ser Ser Leu Glu Tyr Leu Leu Leu Ser Tyr Asn Arg Ile Val	
	195 200 205	
20	aaa ctg gcg cct gag gac ctg gcc aat ctg acc gcc ctg cgt gtg ctc	816
	Lys Leu Ala Pro Glu Asp Leu Ala Asn Leu Thr Ala Leu Arg Val Leu	
	210 215 220	
25	gat gtg ggc gga aat tgc cgc cgc tgc gac cac gct ccc aac ccc tgc	864
	Asp Val Gly Gly Asn Cys Arg Arg Cys Asp His Ala Pro Asn Pro Cys	
	225 230 235 240	
30	atg gag tgc cct cgt cac ttc ccc cag cta cat ccc gat acc ttc agc	912
	Met Glu Cys Pro Arg His Phe Pro Gln Leu His Pro Asp Thr Phe Ser	
	245 250 255	
35	cac ctg agc cgt ctt gaa ggc ctg gtg ttg aag gac agt tct ctc tcc	960
	His Leu Ser Arg Leu Glu Gly Leu Val Leu Lys Asp Ser Ser Leu Ser	
	260 265 270	
40	tgg ctg aat gcc agt tgg ttc cgt ggg ctg gga aac ctc cga gtg ctg	1008
	Trp Leu Asn Ala Ser Trp Phe Arg Gly Leu Gly Asn Leu Arg Val Leu	
	275 280 285	
45	gac ctg agt gag aac ttc ctc tac aaa tgc atc act aaa acc aag gcc	1056
	Asp Leu Ser Glu Asn Phe Leu Tyr Lys Cys Ile Thr Lys Thr Lys Ala	
	290 295 300	
50	ttc cag ggc cta aca cag ctg cgc aag ctt aac ctg tcc ttc aat tac	1104
	Phe Gln Gly Leu Thr Gln Leu Arg Lys Leu Asn Leu Ser Phe Asn Tyr	
	305 310 315 320	
55	caa aag agg gtg tcc tta gcc cac ctg tct ctg gcc cct tcc ttc ggg	1152
	Gln Lys Arg Val Ser Phe Ala His Leu Ser Leu Ala Pro Ser Phe Gly	
	325 330 335	
60	agc ctg gtc gcc ctg aag gag ctg gac atg cac ggc atc ttc ttc cgc	1200
	Ser Leu Val Ala Leu Lys Glu Leu Asp Met His Gly Ile Phe Phe Arg	
	340 345 350	
65	tca ctc gat gag acc acg ctc cgg cca ctg gcc cgc ctg ccc atg ctc	1248
	Ser Leu Asp Glu Thr Thr Leu Arg Pro Leu Ala Arg Leu Pro Met Leu	
	355 360 365	

	cag act ctg cgt ctg cag atg aac ttc atc aac cag gcc cag ctc ggc	1296
	Gln Thr Leu Arg Leu Gln Met Asn Phe Ile Asn Gln Ala Gln Leu Gly	
	370 375 380	
5	atc ttc agg gcc ttc cct ggc ctg cgc tac gtg gac ctg tcg gac aac	1344
	Ile Phe Arg Ala Phe Pro Gly Leu Arg Tyr Val Asp Leu Ser Asp Asn	
	385 390 395 400	
10	cgc atc agc gga gct tcg gag ctg aca gcc acc atg ggg gag gca gat	1392
	Arg Ile Ser Gly Ala Ser Glu Leu Thr Ala Thr Met Gly Glu Ala Asp	
	405 410 415	
15	gga ggg gag aag gtc tgg ctg cag cct ggg gac ctt gct ccg gcc cca	1440
	Gly Gly Glu Lys Val Trp Leu Gln Pro Gly Asp Leu Ala Pro Ala Pro	
	420 425 430	
20	gtg gac act ccc agc tct gaa gac ttc agg ccc aac tgc agc acc ctc	1488
	Val Asp Thr Pro Ser Ser Glu Asp Phe Arg Pro Asn Cys Ser Thr Leu	
	435 440 445	
25	aac ttc acc ttg gat ctg tca cgg aac aac ctg gtg acc gtg cag ccg	1536
	Asn Phe Thr Leu Asp Leu Ser Arg Asn Asn Leu Val Thr Val Gln Pro	
	450 455 460	
30	gag atg ttt gcc cag ctc tcg cac ctg cag tgc ctg cgc ctg agg cac	1584
	Glu Met Phe Ala Gln Leu Ser His Leu Gln Cys Leu Arg Leu Ser His	
	465 470 475 480	
35	aac tgc atc tcg cag gca gtc aat ggc tcc cag ttc ctg ccg ctg acc	1632
	Asn Cys Ile Ser Gln Ala Val Asn Gly Ser Gln Phe Leu Pro Leu Thr	
	485 490 495	
40	ggc ctg cag gtg cta gac ctg tcc cac aat aag ctg gac ctc tac cac	1680
	Gly Leu Gln Val Leu Asp Leu Ser His Asn Lys Leu Asp Leu Tyr His	
	500 505 510	
45	gag cac tca ttc acg gag cta cca cga ctg gag gcc ctg gac ctc agc	1728
	Glu His Ser Phe Thr Glu Leu Pro Arg Leu Glu Ala Leu Asp Leu Ser	
	515 520 525	
50	tac aac agc cag ccc ttt ggc atg cag ggc gtg ggc cac aac ttc agc	1776
	Tyr Asn Ser Gln Pro Phe Gly Met Gln Gly Val Gly His Asn Phe Ser	
	530 535 540	
55	ttc gtg gct cac ctg cgc acc ctg cgc cac ctc agc ctg gcc cac aac	1824
	Phe Val Ala His Leu Arg Thr Leu Arg His Leu Ser Leu Ala His Asn	
	545 550 555 560	
60	aac atc cac agc caa gtg tcc cag cag ctc tgc agt acg tcg ctg cgg	1872
	Asn Ile His Ser Gln Val Ser Gln Gln Leu Cys Ser Thr Ser Leu Arg	
	565 570 575	
65	gcc ctg gac ttc agc ggc aat gca ctg ggc cat atg tgg gcc gag gga	1920
	Ala Leu Asp Phe Ser Gly Asn Ala Leu Gly His Met Trp Ala Glu Gly	
	580 585 590	

		gac	ctc	tat	ctg	cac	ttc	ttc	caa	ggc	ctg	agc	ggt	ttg	atc	tgg	ctg	1968
		Asp	Leu	Tyr	Leu	His	Phe	Phe	Gln	Gly	Leu	Ser	Gly	Leu	Ile	Trp	Leu	
				595					600					605				
5		gac	ttg	tcc	cag	aac	cgc	ctg	cac	acc	ctc	ctg	ccc	caa	acc	ctg	cgc	2016
		Asp	Leu	Ser	Gln	Asn	Arg	Leu	His	Thr	Leu	Leu	Pro	Gln	Thr	Leu	Arg	
			610					615					620					
10		aac	ctc	ccc	aag	agc	cta	cag	gtg	ctg	cgt	ctc	cgt	gac	aat	tac	ctg	2064
		Asn	Leu	Pro	Lys	Ser	Leu	Gln	Val	Leu	Arg	Leu	Arg	Asp	Asn	Tyr	Leu	
			625					630					635				640	
15		gcc	ttc	ttt	aag	tgg	tgg	agc	ctc	cac	ttc	ctg	ccc	aaa	ctg	gaa	gtc	2112
		Ala	Phe	Phe	Lys	Trp	Trp	Ser	Leu	His	Phe	Leu	Pro	Lys	Leu	Glu	Val	
						645						650				655		
20		ctc	gac	ctg	gca	gga	aac	cag	ctg	aag	gcc	ctg	acc	aat	ggc	agc	ctg	2160
		Leu	Asp	Leu	Ala	Gly	Asn	Gln	Leu	Lys	Ala	Leu	Thr	Asn	Gly	Ser	Leu	
					660							665				670		
		cct	gct	ggc	acc	cgg	ctc	cgg	agg	ctg	gat	gtc	agc	tgc	aac	agc	atc	2208
		Pro	Ala	Gly	Thr	Arg	Leu	Arg	Arg	Leu	Asp	Val	Ser	Cys	Asn	Ser	Ile	
					675					680					685			
25		agc	ttc	gtg	gcc	ccc	ggc	ttc	ttt	tcc	aag	gcc	aag	gag	ctg	cga	gag	2256
		Ser	Phe	Val	Ala	Pro	Gly	Phe	Phe	Ser	Lys	Ala	Lys	Glu	Leu	Arg	Glu	
				690				695						700				
30		ctc	aac	ctt	agc	gcc	aac	gcc	ctc	aag	aca	gtg	gac	cac	tcc	tgg	ttt	2304
		Leu	Asn	Leu	Ser	Ala	Asn	Ala	Leu	Lys	Thr	Val	Asp	His	Ser	Trp	Phe	
			705				710					715					720	
35		ggg	ccc	ctg	gcg	agt	gcc	ctg	caa	ata	cta	gat	gta	agc	gcc	aac	cct	2352
		Gly	Pro	Leu	Ala	Ser	Ala	Leu	Gln	Ile	Leu	Asp	Val	Ser	Ala	Asn	Pro	
						725						730				735		
40		ctg	cac	tgc	gcc	tgt	ggg	gcg	gcc	ttt	atg	gac	ttc	ctg	ctg	gag	gtg	2400
		Leu	His	Cys	Ala	Cys	Gly	Ala	Ala	Phe	Met	Asp	Phe	Leu	Leu	Glu	Val	
					740					745						750		
		cag	gct	gcc	gtg	ccc	ggt	ctg	ccc	agc	cgg	gtg	aag	tgt	ggc	agt	ccg	2448
		Gln	Ala	Ala	Val	Pro	Gly	Leu	Pro	Ser	Arg	Val	Lys	Cys	Gly	Ser	Pro	
				755				760						765				
45		ggc	cag	ctc	cag	ggc	ctc	agc	atc	ttt	gca	cag	gac	ctg	cgc	ctc	tgc	2496
		Gly	Gln	Leu	Gln	Gly	Leu	Ser	Ile	Phe	Ala	Gln	Asp	Leu	Arg	Leu	Cys	
				770				775						780				
50		ctg	gat	gag	gcc	ctc	tcc	tgg	gac	tgt	ttc	gcc	ctc	tgc	ctg	ctg	gct	2544
		Leu	Asp	Glu	Ala	Leu	Ser	Trp	Asp	Cys	Phe	Ala	Leu	Ser	Leu	Leu	Ala	
			785					790				795					800	
55		gtg	gct	ctg	ggc	ctg	ggt	gtg	ccc	atg	ctg	cat	cac	ctc	tgt	ggc	tgg	2592
		Val	Ala	Leu	Gly		Gly	Val	Pro	Met	Leu	His	His	Leu	Cys	Gly	Trp	
						805					810					815		

	gac ctc tgg tac tgc ttc cac ctg tgc ctg gcc tgg ctt ccc tgg cgg	2640
	Asp Leu Trp Tyr Cys Phe His Leu Cys Leu Ala Trp Leu Pro Trp Arg	
	820 825 830	
5	ggg cgg caa agt ggg cga gat gag gat gcc ctg ccc tac gat gcc ttc	2688
	Gly Arg Gln Ser Gly Arg Asp Glu Asp Ala Leu Pro Tyr Asp Ala Phe	
	835 840 845	
10	gtg gtc ttc gac aaa acg cag agc gca gtg gca gac tgg gtg tac aac	2736
	Val Val Phe Asp Lys Thr Gln Ser Ala Val Ala Asp Trp Val Tyr Asn	
	850 855 860	
15	gag ctt cgg ggg cag ctg gag gag tgc cgt ggg cgc tgg gca ctc cgc	2784
	Glu Leu Arg Gly Gln Leu Glu Glu Cys Arg Gly Arg Trp Ala Leu Arg	
	865 870 875 880	
20	ctg tgc ctg gag gaa cgc gac tgg ctg cct ggc aaa acc ctc ttt gag	2832
	Leu Cys Leu Glu Gln Arg Asp Trp Leu Pro Gly Lys Thr Leu Phe Glu	
	885 890 895	
25	aac ctg tgg gcc tgc gtc tat ggc agc cgc aag acg ctg ttt gtg ctg	2880
	Asn Leu Trp Ala Ser Val Tyr Gly Ser Arg Lys Thr Leu Phe Val Leu	
	900 905 910	
30	gcc cac acg gac cgg gtc agt ggt ctc ttg cgc gcc agc ttc ctg ctg	2928
	Ala His Thr Asp Arg Val Ser Gly Leu Leu Arg Ala Ser Phe Leu Leu	
	915 920 925	
35	gcc cag cag cgc ctg ctg gag gac cgc aag gac gtc gtg gtg ctg gtg	2976
	Ala Gln Gln Arg Leu Leu Glu Asp Arg Lys Asp Val Val Val Leu Val	
	930 935 940	
40	atc ctg agc cct gac ggc cgc cgc tcc cgc tat gtg cgg ctg cgc cag	3024
	Ile Leu Ser Pro Asp Gly Arg Arg Ser Arg Tyr Val Arg Leu Arg Gln	
	945 950 955 960	
45	cgc ctc tgc cgc cag agt gtc ctc ctc tgg ccc cac cag ccc agt ggt	3072
	Arg Leu Cys Arg Gln Ser Val Leu Leu Trp Pro His Gln Pro Ser Gly	
	965 970 975	
50	cag cgc agc ttc tgg gcc cag ctg ggc atg gcc ctg acc agg gac aac	3120
	Gln Arg Ser Phe Trp Ala Gln Leu Gly Met Ala Leu Thr Arg Asp Asn	
	980 985 990	
55	cac cac ttc tat aac cgg aac ttc tgc cag gga ccc acg gcc gaa tag	3168
	His His Phe Tyr Asn Arg Asn Phe Cys Gln Gly Pro Thr Ala Glu	
	995 1000 1005	

MPMKWSGWRWSWGPATHTALPPPQGFCSALHPLSLVQAIMLAMTLALGTLPAFLPCELQPHGLVNCN
 WLFLKSVPHFMAAPRGNTVSLSLSSNRIHHLHDSDFAHLP SLRHLNLKWNCPFVGLSPMHFPCHMTIE
 PSTFLAVPTLEELNLSYNNIMTVPALPKSLISLSLHSTNIIIMLDSASLAGLHALRFLFMDGNCYYKNPC
 5 RQALEVAPGALLGLGNLTHLSLKYNNTLVVPRNLPSSELYLLLSYNRIVKLAPEDLANLTALRVLDVGG
 NCRRCDHAPNPCMECFRHF PQLHPDTFHSLSRLEGLVLKDSLSWLNASWFRGLGNLRVLDLSENFLYK
 CITKTKAFQGLTQLRKLNLSFNYSQKRVSFHLSLAPSPGSLVALKELDMHGIFFRSLDETTLRPLARLP
 MLQTLRLQMNFINQAQLGIFRAPFGLRYVDLSNDRISGASELTATMGEADGGGEKVWLQPGDLAPAPVDT
 PSSSEDFRPNCSLTNFTLDLSRNNLVTVQPEMFAQLSHLQCLRLSHNCISQAVNGSQFLPLTGLQVLDLS
 10 HNKLDLYHEHSFTLPRLEALDLSYNSQPFQMGVGHNF SFVAHLRTRLRHLSLAHNNIHSQVVSQQLCST
 SLRALDFSGNALGHMWAEGDLYLHFFQGLSGLIWLDSLQNLRLHTLLPQTLRNLPKSLQVLRRLRDNYLAF
 PKWWSLHFLPKLEVLDLAGNQLKALTNGSLPAGTRLRRLDVSNCNSISFVAPGFFSKAKELRELNLSANA
 LKTVDHSWFGPLASALQILDVSANPLHCACGAAMFMDPLEVQAAVPGLP SRVKCGSPGQLQGLSIFAQD
 LRLCLDEALSWDCFALSLLAVALGLGVFMLHHLCGWDLWYCFHLCLAWLPWRGRQSGRDEDALPYDAFV
 15 VFDKTSASAVADWVYNELRGQLEECRGRWALRLCLEERDWLP GKTLFENLWASVYGSRKTLFVLAHTDRV
 SGLLRASFLLAQQRLLDRKDVVVLVILSPDGRRSRYVRLRQRLCRQSVLLWPHQPSGQRSFWAQLGMA
 LTRDNHHFYNRNFCQGPTAE

partial rodent, e.g., mouse DTLR10 nucleotide sequence (SEQ ID NO: 35):

20 TGGCCACAC GGACCGCGTC AGTGGCCTCC TGGCACCAG CTTCTGCTG GCTCAGCAGC 60
 GCCTGTTGGA AGACCGCAAG GACGTGGTGG TGTGGGTGAT CCTGCGTCCG GATGCCCCAC 120
 25 CGTCCCGCTA TGTGCGACTG CGCCAGCGTC TCTGCCGCCA GAGTGTGCTC TTCTGCCCCC 180
 AGCGACCCAA CGGECAGGGG GGCTTCTGGG CCCAGCTGAG TACAGCCCTG ACTAGGGACA 240
 ACCGCCACTT CTATAACCAG AACTTCTGCC GGGGACCTAC AGCAGAATAG CTCAGAGCAA 300
 30 CAGCTGGAAA CAGCTGCATC TTCATGTCTG GTTCCCGAGT TGCTCTGCCT GCCTTGCTCT 360
 GTCTTACTAC ACCGCTATTT GGCAAGTGCG CAATATATGC TACCAAGCCA CCAGGCCAC 420
 35 GGAGCAAAGG TTGGCTGTAA AGGCTAGTTT TCTTCCCATG CATCTTCAG GAGAGTGAAG 480
 ATAGACACCA AACCCAC 497

40 Further rodent, e.g., mouse, DTLR10 (SEQ ID NO: 44 and 45):

aac ctg tcc ttc aat tac cgc aag aag gta tcc ttt gcc cgc ctc cac 48
 Asn Leu Ser Phe Asn Tyr Arg Lys Lys Val Ser Phe Ala Arg Leu His
 1 5 10 15

45 ctg gca agt tcc ttt aag aac ctg gtg tca ctg cag gag ctg aac atg 96
 Leu Ala Ser Ser Phe Lys Asn Leu Val Ser Leu Gln Glu Leu Asn Met
 20 25 30

50 aac ggc atc ttc ttc cgc ttg ctc aac aag tac acg ctc aga tgg ctg 144
 Asn Gly Ile Phe Phe Arg Leu Leu Asn Lys Tyr Thr Leu Arg Trp Leu
 35 40 45

55 gcc gat ctg ccc aaa ctc cac act ctg cat ctt caa atg aac ttc atc 192
 Ala Asp Leu Pro Lys Leu His Thr Leu His Leu Gln Met Asn Phe Ile
 50 55 60

	aac cag gca cag ctc agc atc ttt ggt acc ttc cga gcc ctt cgc ttt	240
	Asn Gln Ala Gln Leu Ser Ile Phe Gly Thr Phe Arg Ala Leu Arg Phe	
	65 70 75 80	
5	gtg gac ttg tca gac aat cgc atc agt cgg cct tca acg ctg tca gaa	288
	Val Asp Leu Ser Asp Asn Arg Ile Ser Gly Pro Ser Thr Leu Ser Glu	
	85 90 95	
10	gcc acc cct gaa gag gca gat gat gca gag cag gag gag ctg ttg tct	336
	Ala Thr Pro Glu Glu Ala Asp Asp Ala Glu Gln Glu Glu Leu Leu Ser	
	100 105 110	
15	gcg gat cct cac cca gct ccg ctg agc acc cct gct tct aag aac ttc	384
	Ala Asp Pro His Pro Ala Pro Leu Ser Thr Pro Ala Ser Lys Asn Phe	
	115 120 125	
20	atg gac agg tgt aag aac ttc aag ttc aac atg gac ctg tct cgg aac	432
	Met Asp Arg Cys Lys Asn Phe Lys Phe Asn Met Asp Leu Ser Arg Asn	
	130 135 140	
25	aac ctg gtg act atc aca gca gag atg ttt gta aat ctc tca cgc ctc	480
	Asn Leu Val Thr Ile Thr Ala Glu Met Phe Val Asn Leu Ser Arg Leu	
	145 150 155 160	
30	cag tgt ctt agc ctg agc cac aac tca att gca cag gct gtc aat ggc	528
	Gln Cys Leu Ser Leu Ser His Asn Ser Ile Ala Gln Ala Val Asn Gly	
	165 170 175	
35	tct cag ttc ctg ccg ctg acc ggt ctg cag gtg cta gac ctg tcc cac	576
	Ser Gln Phe Leu Pro Leu Thr Gly Leu Gln Val Leu Asp Leu Ser His	
	180 185 190	
40	aat aag ctg gac ctc tac cac gag cac tca ttc acg gag cta cca cga	624
	Asn Lys Leu Asp Leu Tyr His Glu His Ser Phe Thr Glu Leu Pro Arg	
	195 200 205	
45	ctg gag gcc ctg gac ctc agc tac aac agc cag ccc ttt agc atg aag	672
	Leu Glu Ala Leu Asp Leu Ser Tyr Asn Ser Gln Pro Phe Ser Met Lys	
	210 215 220	
50	ggt ata ggc cac aat ttc agt ttt gtg acc cat ctg tcc atg cta cag	720
	Gly Ile Gly His Asn Phe Ser Phe Val Thr His Leu Ser Met Leu Gln	
	225 230 235 240	
55	agc ctt agc ctg gca cac aat gac att cat acc cgt gtg tcc tca cat	768
	Ser Leu Ser Leu Ala His Asn Asp Ile His Thr Arg Val Ser Ser His	
	245 250 255	
60	ctc aac agc aac tca gtg agg ttt ctt gac ttc agc ggc aac ggt atg	816
	Leu Asn Ser Asn Ser Val Arg Phe Leu Asp Phe Ser Gly Asn Gly Met	
	260 265 270	
65	ggc cgc atg tgg gat gag ggg ggc ctt tat ctc cat ttc ttc caa ggc	864
	Gly Arg Met Trp Asp Glu Gly Gly Leu Tyr Leu His Phe Phe Gln Gly	
	275 280 285	

	ctg agt ggc gtg ctg aag ctg gac ctg tct caa aat aac ctg cat atc	912
	Leu Ser Gly Val Leu Lys Leu Asp Leu Ser Gln Asn Asn Leu His Ile	
	290 295 300	
5	ctc cgg ccc cag aac ctt gac aac ctc ccc aag agc ctg aag ctg ctg	960
	Leu Arg Pro Gln Asn Leu Asp Asn Leu Pro Lys Ser Leu Lys Leu Leu	
	305 310 315 320	
10	agc ctc cga gac aac tac cta tct ttc ttt aac tgg acc agt ctg tcc	1008
	Ser Leu Arg Asp Asn Tyr Leu Ser Phe Phe Asn Trp Thr Ser Leu Ser	
	325 330 335	
15	ttc cta ccc aac ctg gaa gtc cta gac ctg gca ggc aac cag cta aag	1056
	Phe Leu Pro Asn Leu Glu Val Leu Asp Leu Ala Gly Asn Gln Leu Lys	
	340 345 350	
20	gcc ctg acc aat ggc acc ctg cct aat ggc acc ctc ctc cag aaa ctc	1104
	Ala Leu Thr Asn Gly Thr Leu Pro Asn Gly Thr Leu Leu Gln Lys Leu	
	355 360 365	
	gat gtc agt agc aac agt atc gtc tct gtg gcc ccc ggc ttc ttt tcc	1152
	Asp Val Ser Ser Asn Ser Ile Val Ser Val Ala Pro Gly Phe Phe Ser	
	370 375 380	
25	aag gcc aag gag ctg cga gag ctc aac ctt agc gcc aac gcc ctc aag	1200
	Lys Ala Lys Glu Leu Arg Glu Leu Asn Leu Ser Ala Asn Ala Leu Lys	
	385 390 395 400	
30	aca gtg gac cac tcc tgg ttt ggg ccc att gtg atg aac ctg aca gtt	1248
	Thr Val Asp His Ser Trp Phe Gly Pro Ile Val Met Asn Leu Thr Val	
	405 410 415	
35	cta gac gtg aga agc aac cct ctg cac tgt gcc tgt ggg gca gcc ttc	1296
	Leu Asp Val Arg Ser Asn Pro Leu His Cys Ala Cys Gly Ala Ala Phe	
	420 425 430	
	gta gac tta ctg ttg gag gtg cag acc aag gtg cct ggc ctg gct aat	1344
	Val Asp Leu Leu Leu Glu Val Gln Thr Lys Val Pro Gly Leu Ala Asn	
	435 440 445	
40	ggt gtg aag tgt ggc agc ccc ggc cag ctg cag ggc cgt agc atc ttc	1392
	Gly Val Lys Cys Gly Ser Pro Gly Gln Leu Gln Gly Arg Ser Ile Phe	
	450 455 460	
45	gcg cag gac ctg cgg ctg tgc ctg gat gag gtc ctc tct tgg gac tgc	1440
	Ala Gln Asp Leu Arg Leu Cys Leu Asp Glu Val Leu Ser Trp Asp Cys	
	465 470 475 480	
50	ttt ggc ctt tca ctc ttg gct gtg gcc gtg ggc atg gtg gtg cct ata	1488
	Phe Gly Leu Ser Leu Leu Ala Val Ala Val Gly Met Val Val Pro Ile	
	485 490 495	
55	ctg cac cat ctc tgc ggc tgg gac gtc tgg tac tgt ttt cat ctg tgc	1536
	Leu His His Leu Cys Gly Trp Asp Val Trp Tyr Cys Phe His Leu Cys	
	500 505 510	

	ctg gca tgg cta cct ttg cta gcc cgc agc cga cgc agc gcc caa act	1584
	Leu Ala Trp Leu Pro Leu Leu Ala Arg Ser Arg Arg Ser Ala Gln Thr	
	515 520 525	
5	ctc cct tat gat gcc ttc gtg gtg ttc gat aag gca cag agc gca gtt	1632
	Leu Pro Tyr Asp Ala Phe Val Val Phe Asp Lys Ala Gln Ser Ala Val	
	530 535 540	
10	gcc gac tgg gtg tat aac gag ctg cgg gtg cgg ctg gag gag cgg cgc	1680
	Ala Asp Trp Val Tyr Asn Glu Leu Arg Val Arg Leu Glu Glu Arg Arg	
	545 550 555 560	
15	ggc cgc tgg gca ctc cgc ctg tgc ctg gag gac cga gat tgg ctg cct	1728
	Gly Arg Trp Ala Leu Arg Leu Cys Leu Glu Asp Arg Asp Trp Leu Pro	
	565 570 575	
20	ggc cag acg ctc ttc gag aac ctc tgg gct tcc atc tac ggg agc cgc	1776
	Gly Gln Thr Leu Phe Glu Asn Leu Trp Ala Ser Ile Tyr Gly Ser Arg	
	580 585 590	
25	aag act cta ttt gtg ctg gcc cac acg gac cgc gtc agt cgc ctc ctg	1824
	Lys Thr Leu Phe Val Leu Ala His Thr Asp Arg Val Ser Gly Leu Leu	
	595 600 605	
30	cgc acc agc ttc ctg ctg gct cag cag cgc ctg ttg gaa gac cgc aag	1872
	Arg Thr Ser Phe Leu Leu Ala Gln Gln Arg Leu Leu Glu Asp Arg Lys	
	610 615 620	
35	gac gtg gtg gtg ttg gtg acc ctg cgt ccg gat gcc cac cgc tcc cgc	1920
	Asp Val Val Val Leu Val Ile Leu Arg Pro Asp Ala His Arg Ser Arg	
	625 630 635 640	
40	tat gtg cga ctg cgc cag cgt ctc tgc cgc cag agt gtg ctc ttc tgg	1968
	Tyr Val Arg Leu Arg Gln Arg Leu Cys Arg Gln Ser Val Leu Phe Trp	
	645 650 655	
45	ccc cag cag ccc aac ggg cag ggg ggc ttc tgg gcc cag ctg agt aca	2016
	Pro Gln Gln Pro Asn Gly Gln Gly Gly Phe Trp Ala Gln Leu Ser Thr	
	660 665 670	
50	gcc ctg act agg gac aac cgc cac ttc tat aac cag aac ttc tgc cgg	2064
	Ala Leu Thr Arg Asp Asn Arg His Phe Tyr Asn Gln Asn Phe Cys Arg	
	675 680 685	
55	gga cct aca gca gaa tagctcagag caacagctgg aaacagctgc atcttcatgt	2119
	Gly Pro Thr Ala Glu	
	690	
60	ctgggtcccg agttgctctg cctgccttgc tctgtcttac tacaccgcta tttggcaagt	2179
	gcgcaatata tgctaccaag ccaccaggcc cacggagcaa aggttggctg taaaggctag	2239
	ttttcttccc atgcatcttt caggagagtg aagatagaca ccaaaccac	2289

NLSFNRYRKKVSPARLHLASSFKNLVSLQELNMNGIFFRLLNKYTLRWLADLPKLHTLHLQMNFINQAQL
SIFGTFRALRFVDLSDNRI SG PSTLSEATPEEADDAEQEELLSADPHAPLSTPASKNFMORCKNFKFN
MDLSRNNLVTTAEMFVNLSRLQCLSLSHNSIAQAVNGSQFLPLTGLQVLDLSHNKLDLYHEHSFTFLP
5 RLEALDLSYNSQPF SMK GIGHNFSFVTHLSMLQSLSLAHNDIHTRVSSHLSNSVRF LDFSGNGMGRMW
DEGGLYLHFFQGLSGVLKLDLSQNNLHILRPQNLNLPKSLKLLSLRDNYLSFFNWTSLSF LPNLEVLD
LAGNQLKALTNGTL PNGTLLQKLDVSSNSIVSVAPGFFSKAKELRELNLSANALKTV DHSWFGPIVMNL
TVLDVRSNPLHCACGAA FVDLLLEVQTKVPGLANGVKCGSPGQLQGRSIFAQDLRLCLDEVLSWDCFGL
SLLAVAVGMVVPILHHLCCGWDVWYCFHLCLAWLP LLARSRRSAQTLFYDAFVVF DKAQSAVADWVYNEL
10 RVRLEERRGRWALRLCLEDRDWLPGQTLFENLWASTYGSRKTLFVLAHTDRVSGLLRTSFLLAQQRLLE
DRKDVVVLVTLRPDAHRSRYVRLRQRLCRQSVLFWPQQPNGGGFWAQLSTALTRDNRHFYNQNF CRGP
TAE

Table 11: Comparison of intracellular domains of human DTLRs. DTLR1 is SEQ ID NO: 2; DTLR2 is SEQ ID NO: 4; DTLR3 is SEQ ID NO: 6; DTLR4 is SEQ ID NO: 8; DTLR5 is SEQ ID NO: 10; and DTLR6 is SEQ ID NO: 12. Particularly important and conserved, e.g., characteristic, residues correspond, across the DTLRs, to SEQ ID NO: 18 residues tyr10-tyr13; trp26; cys46; trp52; pro54-gly55; ser69; lys71; trp134-pro135; and phe144-trp145.

10	DTLR1	QRNLQFHAFISYSGHD---SFWVKNELLPNLEKEG-----MQICLHERNF
	DTLR9	KENLQFHAFISYSEHD---SAWVKSELVPYLEKED-----IQICLHERNF
	DTLR8	-----NELIPNLEKEDGS---ILICLYESYF
	DTLR2	SRNICYDAFVSYSERD---AYWVENLMVQELFNFP---FKLCCLKRDF
	DTLR6	SPDCCYDAFIVYDTKDPVTEWVLAELVAKLEDPREK---HFNLCLEERDW
	DTLR7	TSQTFYDAYISYDTKQASVTDWVINELRHLEESRDK---NVLLCLEERDW
15	DTLR10	EDALPYDAFVVFDTKXSAVADWVYNELRGQLEECRGRW---ALRLCLEERDW
	DTLR4	RGNIYDAFVIYSSQD---EDWVRNELVKNLEEGVPP---FQLCLHYRDF
	DTLR5	PDMYKYDAYLCFSSKD---FTWVQNALLKHLDTQYSDQNRNLCFEERDF
	DTLR3	TEQFEYAAYIIHAYKD---KDWVWEHFSSMEKEDQS-----LKFCLEERDF
		: . . . : :
20	DTLR1	VPGKSIVENIITC-IEKSYKSI FVLSPNFVQSEWCH-YELYFAHNNLFHE
	DTLR9	VPGKSIVENIINC-IEKSYKSI FVLSPNFVQSEWCH-YELYFAHNNLFHE
	DTLR8	DPGKSISENIVSF-IEKSYKSI FVLSPNFVQSEWCH-YELYFAHNNLFHE
	DTLR2	IPGKWIIDNIIDS-IEKSHKTVFVLSNFVQSEWCK-YELDFSHFRLFEE
25	DTLR6	LPGQPVLENLSQS-IQLSKKTVFVMTDKYAKTENFK-IAFYLSHORLMDE
	DTLR7	DPLGLAIDNLMQS-INQSKKTVFVLTKKYAKSNKFX-TAFYLLXLRMLGE
	DTLR10	LPGKTLFENLWAS-VYGSRKTLFVLAHTDRVSGLLR-AIFLLAQQRLLF-
	DTLR4	IPGVAIAANIIEGFEHKSARKVIVVVSQHFQSRWCI-FEYETIAQTWQFLS
	DTLR5	VPGENRIANIQDA-IWNSRKIVCLVSRHFLRDGWCL-EAFSYAQGRCLSD
30	DTLR3	EAGVFELEAIVNS-IKRSRKIEFVITHHLLKDPCKRFKVHHAQQAEQ
		. * : . * * : : :
	DTLR1	GSNSLILILLEPI PQYSIPSSYHKLKSLMARRTYLEWPKEKSKRGLFWAN
	DTLR9	GSNNLILILLEPI PQNSIPNKYHKLKALMTQRTYLQWPKEKSKRGLFWA-
35	DTLR8	NSDHIILILLEPI PFYCIPTRYHKLKALLEKKAYLEWPKDRRKCGLFWAN
	DTLR2	NNDAAIILILLEPI EKKAIPQRFCKLRKIMNTKTYLEWPMDEAQREGFWVN
	DTLR6	KVDVILIFLEKPFQK---SKFLQLRKRLCGSSVLEWPTNPQAHPIFWQC
	DTLR7	NMDVIIIFILLEPVLQH---SPYLRRLRQRICKSSILQWPDNPKAERLFWQT
	DTLR10	-----
40	DTLR4	SRAGIIFIVLQKVEKT-LLRQQVELYRLLSRNTYLEWEDSVLGRHIFWRR
	DTLR5	LNSALIMVVVGSLSQY-QLMKHQSI RGFVQKQYLRNPEDLQDVGWFLHK
	DTLR3	NLOSIILVFLEEIPDYKLNHALCLRRGMFKSHCILNWPVQKERIGAFRHK

45	DTLR1	LRAAINIKLTEQAKK-----
	DTLR9	-----
	DTLR8	LRAAVNVNVLATREMYELQTFTELNEESRGSTISLMRTDCL
	DTLR2	LRAAIKS-----
	DTLR6	LKNALATDNHVAYSQVFKETV-----
50	DTLR7	LXNVVLTENDSRYNMYVDSIKQY-----
	DTLR10	-----
	DTLR4	LRKALLDGKSWNPEGTVGTGCNWQEATSI-----
	DTLR5	LSQQILKKEKEKKKDNNIPLQTVATIS-----
55	DTLR3	LQVALGSKNSVH-----

Transmembrane segments correspond approximately to 802-818 (791-823) of primate DTLR7 SEQ ID NO: 37; 559-575 (550-586) of DTLR8 SEQ ID NO: 39; 553-569 (549-582) of DTLR9 SEQ ID NO: 41; 796-810 (790-814) of DTLR10 SEQ ID NO: 43; and 481-497 (475-503) of DTLR10 SEQ ID NO: 45.

As used herein, the term DNAX Toll like receptor 2 (DTLR2) shall be used to describe a protein comprising a protein or peptide segment having or sharing the amino acid sequence shown in Table 2, or a substantial fragment thereof. Similarly, with a DTLR3 and Table 3; DTLR4 and Table 4; DTLR5 and Table 5; DTLR6 and Table 6; DTLR7 and Table 7; DTLR8 and Table 8; DTLR9 and Table 9; and DTLR10 and Table 10. Rodent, e.g., mouse, DTLR11 sequence is provided, e.g., in EST AA739083; DTLR13 in ESTAI019567; DTLR14 in ESTs AI390330 and AA244663.

The invention also includes a protein variations of the respective DTLR allele whose sequence is provided, e.g., a mutein agonist or antagonist. Typically, such agonists or antagonists will exhibit less than about 10% sequence differences, and thus will often have between 1- and 11-fold substitutions, e.g., 2-, 3-, 5-, 7-fold, and others. It also encompasses allelic and other variants, e.g., natural polymorphic, of the protein described. Typically, it will bind to its corresponding biological receptor with high affinity, e.g., at least about 100 nM, usually better than about 30 nM, preferably better than about 10 nM, and more preferably at better than about 3 nM. The term shall also be used herein to refer to related naturally occurring forms, e.g., alleles, polymorphic variants, and metabolic variants of the mammalian protein.

This invention also encompasses proteins or peptides having substantial amino acid sequence identity with the amino acid sequence in Table 2. It will include sequence variants with relatively few substitutions, e.g., preferably less than about 3-5. Similar features apply to

the other DTLR sequences provided in Tables 3, 4, 5, 6, 7, 8, 9, or 10.

A substantial polypeptide "fragment", or "segment", is a stretch of amino acid residues, of at least about 8 amino acids, generally at least 10 amino acids, more generally at least 12 amino acids, often at least 14 amino acids, more often at least 16 amino acids, typically at least 18 amino acids, more typically at least 20 amino acids, usually at least 22 amino acids, more usually at least 24 amino acids, preferably at least 26 amino acids, more preferably at least 28 amino acids, and, in particularly preferred embodiments, at least about 30 or more amino acids. Sequences of segments of different proteins can be compared to one another over appropriate length stretches.

Amino acid sequence homology, or sequence identity, is determined by optimizing residue matches, if necessary, by introducing gaps as required. See, e.g., Needleham, et al., (1970) J. Mol. Biol. 48:443-453; Sankoff, et al., (1983) chapter one in Time Warps, String Edits, and Macromolecules: The Theory and Practice of Sequence Comparison, Addison-Wesley, Reading, MA; and software packages from IntelliGenetics, Mountain View, CA; the University of Wisconsin Genetics Computer Group (GCG), Madison, WI; and the NCBI (NIH); each of which is incorporated herein by reference. This changes when considering conservative substitutions as matches. Conservative substitutions typically include substitutions within the following groups: glycine, alanine; valine, isoleucine, leucine; aspartic acid, glutamic acid; asparagine, glutamine; serine, threonine; lysine, arginine; and phenylalanine, tyrosine. Homologous amino acid sequences are intended to include natural allelic and interspecies variations in the cytokine sequence. Typical homologous proteins or peptides will have from 50-100% homology (if gaps can be introduced), to 60-100% homology

(if conservative substitutions are included) with an amino acid sequence segment of Table 2, 3, 4, 5, 6, 7, 8, 9, or 10. Homology measures will be at least about 70%, generally at least 76%, more generally at least 81%, often at least 85%, more often at least 88%, typically at least 90%, more typically at least 92%, usually at least 94%, more usually at least 95%, preferably at least 96%, and more preferably at least 97%, and in particularly preferred embodiments, at least 98% or more. The degree of homology will vary with the length of the compared segments. Homologous proteins or peptides, such as the allelic variants, will share most biological activities with the embodiments described in Table 2, 3, 4, 6, 7, 8, 9, or 10. Particularly interesting regions of comparison, at the amino acid or nucleotide levels, correspond to those within each of the blocks 1-10, or intrablock regions, corresponding to those indicated in Figures 2A-2B.

As used herein, the term "biological activity" is used to describe, without limitation, effects on inflammatory responses, innate immunity, and/or morphogenic development by respective ligands. For example, these receptors should, like IL-1 receptors, mediate phosphatase or phosphorylase activities, which activities are easily measured by standard procedures. See, e.g., Hardie, et al. (eds. 1995) The Protein Kinase FactBook vols. I and II, Academic Press, San Diego, CA; Hanks, et al. (1991) Meth. Enzymol. 200:38-62; Hunter, et al. (1992) Cell 70:375-388; Lewin (1990) Cell 61:743-752; Pines, et al. (1991) Cold Spring Harbor Symp. Quant. Biol. 56:449-463; and Parker, et al. (1993) Nature 363:736-738. The receptors exhibit biological activities much like regulatable enzymes, regulated by ligand binding. However, the enzyme turnover number is more close to an enzyme than a receptor complex. Moreover, the numbers of occupied receptors necessary to induce such enzymatic

activity is less than most receptor systems, and may number closer to dozens per cell, in contrast to most receptors which will trigger at numbers in the thousands per cell. The receptors, or portions thereof, may be
5 useful as phosphate labeling enzymes to label general or specific substrates.

The terms ligand, agonist, antagonist, and analog of, e.g., a DTLR, include molecules that modulate the characteristic cellular responses to Toll ligand like
10 proteins, as well as molecules possessing the more standard structural binding competition features of ligand-receptor interactions, e.g., where the receptor is a natural receptor or an antibody. The cellular responses likely are mediated through binding of various Toll
15 ligands to cellular receptors related to, but possibly distinct from, the type I or type II IL-1 receptors. See, e.g., Belvin and Anderson (1996) Ann. Rev. Cell Dev. Biol. 12:393-416; Morisato and Anderson (1995) Ann. Rev. Genetics 29:371-3991 and Hultmark (1994) Nature 367:116-
20 117.

Also, a ligand is a molecule which serves either as a natural ligand to which said receptor, or an analog thereof, binds, or a molecule which is a functional analog of the natural ligand. The functional analog may be a
25 ligand with structural modifications, or may be a wholly unrelated molecule which has a molecular shape which interacts with the appropriate ligand binding determinants. The ligands may serve as agonists or antagonists, see, e.g., Goodman, et al. (eds. 1990)
30 Goodman & Gilman's: The Pharmacological Bases of Therapeutics, Pergamon Press, New York.

Rational drug design may also be based upon structural studies of the molecular shapes of a receptor or antibody and other effectors or ligands. Effectors may
35 be other proteins which mediate other functions in response to ligand binding, or other proteins which

normally interact with the receptor. One means for determining which sites interact with specific other proteins is a physical structure determination, e.g., x-ray crystallography or 2 dimensional NMR techniques.

5 These will provide guidance as to which amino acid residues form molecular contact regions. For a detailed description of protein structural determination, see, e.g., Blundell and Johnson (1976) Protein Crystallography, Academic Press, New York, which is hereby incorporated
10 herein by reference.

II. Activities

The Toll like receptor proteins will have a number of different biological activities, e.g., in phosphate
15 metabolism, being added to or removed from specific substrates, typically proteins. Such will generally result in modulation of an inflammatory function, other innate immunity response, or a morphological effect. The DTLR2, 3, 4, 5, 6, 7, 8, 9, or 10 proteins are homologous
20 to other Toll like receptor proteins, but each have structural differences. For example, a human DTLR2 gene coding sequence probably has about 70% identity with the nucleotide coding sequence of mouse DTLR2. At the amino acid level, there is also likely to be reasonable
25 identity.

The biological activities of the DTLRs will be related to addition or removal of phosphate moieties to substrates, typically in a specific manner, but occasionally in a non specific manner. Substrates may be
30 identified, or conditions for enzymatic activity may be assayed by standard methods, e.g., as described in Hardie, et al. (eds. 1995) The Protein Kinase FactBook vols. I and II, Academic Press, San Diego, CA; Hanks, et al. (1991) Meth. Enzymol. 200:38-62; Hunter, et al. (1992) Cell
35 70:375-388; Lewin (1990) Cell 61:743-752; Pines, et al.

(1991) Cold Spring Harbor Symp. Quant. Biol. 56:449-463;
and Parker, et al. (1993) Nature 363:736-738.

III. Nucleic Acids

5 This invention contemplates use of isolated nucleic acid or fragments, e.g., which encode these or closely related proteins, or fragments thereof, e.g., to encode a corresponding polypeptide, preferably one which is biologically active. In addition, this invention covers
10 isolated or recombinant DNA which encodes such proteins or polypeptides having characteristic sequences of the respective DTLRs, individually or as a group. Typically, the nucleic acid is capable of hybridizing, under appropriate conditions, with a nucleic acid sequence
15 segment shown in Tables 2-10, but preferably not with a corresponding segment of Table 1. Said biologically active protein or polypeptide can be a full length protein, or fragment, and will typically have a segment of amino acid sequence highly homologous to one shown in
20 Tables 2-10. Further, this invention covers the use of isolated or recombinant nucleic acid, or fragments thereof, which encode proteins having fragments which are equivalent to the DTLR2-10 proteins. The isolated nucleic acids can have the respective regulatory sequences in the
25 5' and 3' flanks, e.g., promoters, enhancers, poly-A addition signals, and others from the natural gene.

 An "isolated" nucleic acid is a nucleic acid, e.g., an RNA, DNA, or a mixed polymer, which is substantially pure, e.g., separated from other components which
30 naturally accompany a native sequence, such as ribosomes, polymerases, and flanking genomic sequences from the originating species. The term embraces a nucleic acid sequence which has been removed from its naturally occurring environment, and includes recombinant or cloned
35 DNA isolates, which are thereby distinguishable from naturally occurring compositions, and chemically

synthesized analogs or analogs biologically synthesized by heterologous systems. A substantially pure molecule includes isolated forms of the molecule, either completely or substantially pure.

5 An isolated nucleic acid will generally be a homogeneous composition of molecules, but will, in some embodiments, contain heterogeneity, preferably minor. This heterogeneity is typically found at the polymer ends or portions not critical to a desired biological function
10 or activity.

 A "recombinant" nucleic acid is typically defined either by its method of production or its structure. In reference to its method of production, e.g., a product made by a process, the process is use of recombinant
15 nucleic acid techniques, e.g., involving human intervention in the nucleotide sequence. Typically this intervention involves in vitro manipulation, although under certain circumstances it may involve more classical animal breeding techniques. Alternatively, it can be a
20 nucleic acid made by generating a sequence comprising fusion of two fragments which are not naturally contiguous to each other, but is meant to exclude products of nature, e.g., naturally occurring mutants as found in their natural state. Thus, for example, products made by
25 transforming cells with any unnaturally occurring vector is encompassed, as are nucleic acids comprising sequence derived using any synthetic oligonucleotide process. Such a process is often done to replace a codon with a
30 redundant codon encoding the same or a conservative amino acid, while typically introducing or removing a restriction enzyme sequence recognition site. Alternatively, the process is performed to join together nucleic acid segments of desired functions to generate a single genetic entity comprising a desired combination of
35 functions not found in the commonly available natural forms, e.g., encoding a fusion protein. Restriction

enzyme recognition sites are often the target of such artificial manipulations, but other site specific targets, e.g., promoters, DNA replication sites, regulation sequences, control sequences, or other useful features may be incorporated by design. A similar concept is intended for a recombinant, e.g., fusion, polypeptide. This will include a dimeric repeat. Specifically included are synthetic nucleic acids which, by genetic code redundancy, encode equivalent polypeptides to fragments of DTLR2-5 and fusions of sequences from various different related molecules, e.g., other IL-1 receptor family members.

A "fragment" in a nucleic acid context is a contiguous segment of at least about 17 nucleotides, generally at least 21 nucleotides, more generally at least 25 nucleotides, ordinarily at least 30 nucleotides, more ordinarily at least 35 nucleotides, often at least 39 nucleotides, more often at least 45 nucleotides, typically at least 50 nucleotides, more typically at least 55 nucleotides, usually at least 60 nucleotides, more usually at least 66 nucleotides, preferably at least 72 nucleotides, more preferably at least 79 nucleotides, and in particularly preferred embodiments will be at least 85 or more nucleotides. Typically, fragments of different genetic sequences can be compared to one another over appropriate length stretches, particularly defined segments such as the domains described below.

A nucleic acid which codes for a DTLR2-10 will be particularly useful to identify genes, mRNA, and cDNA species which code for itself or closely related proteins, as well as DNAs which code for polymorphic, allelic, or other genetic variants, e.g., from different individuals or related species. Preferred probes for such screens are those regions of the interleukin which are conserved between different polymorphic variants or which contain nucleotides which lack specificity, and will preferably be full length or nearly so. In other situations,

polymorphic variant specific sequences will be more useful.

This invention further covers recombinant nucleic acid molecules and fragments having a nucleic acid
5 sequence identical to or highly homologous to the isolated DNA set forth herein. In particular, the sequences will often be operably linked to DNA segments which control transcription, translation, and DNA replication. These additional segments typically assist in expression of the
10 desired nucleic acid segment.

Homologous, or highly identical, nucleic acid sequences, when compared to one another or Table 2-10 sequences, exhibit significant similarity. The standards for homology in nucleic acids are either measures for
15 homology generally used in the art by sequence comparison or based upon hybridization conditions. Comparative hybridization conditions are described in greater detail below.

Substantial identity in the nucleic acid sequence
20 comparison context means either that the segments, or their complementary strands, when compared, are identical when optimally aligned, with appropriate nucleotide insertions or deletions, in at least about 60% of the nucleotides, generally at least 66%, ordinarily at least
25 71%, often at least 76%, more often at least 80%, usually at least 84%, more usually at least 88%, typically at least 91%, more typically at least about 93%, preferably at least about 95%, more preferably at least about 96 to 98% or more, and in particular embodiments, as high at
30 about 99% or more of the nucleotides, including, e.g., segments encoding structural domains such as the segments described below. Alternatively, substantial identity will exist when the segments will hybridize under selective hybridization conditions, to a strand or its complement,
35 typically using a sequence derived from Tables 2-10. Typically, selective hybridization will occur when there

is at least about 55% homology over a stretch of at least about 14 nucleotides, more typically at least about 65%, preferably at least about 75%, and more preferably at least about 90%. See, Kanehisa (1984) Nucl. Acids Res. 12:203-213, which is incorporated herein by reference.

5 The length of homology comparison, as described, may be over longer stretches, and in certain embodiments will be over a stretch of at least about 17 nucleotides, generally at least about 20 nucleotides, ordinarily at least about

10 24 nucleotides, usually at least about 28 nucleotides, typically at least about 32 nucleotides, more typically at least about 40 nucleotides, preferably at least about 50 nucleotides, and more preferably at least about 75 to 100 or more nucleotides.

15 Stringent conditions, in referring to homology in the hybridization context, will be stringent combined conditions of salt, temperature, organic solvents, and other parameters typically controlled in hybridization reactions. Stringent temperature conditions will usually

20 include temperatures in excess of about 30° C, more usually in excess of about 37° C, typically in excess of about 45° C, more typically in excess of about 55° C, preferably in excess of about 65° C, and more preferably in excess of about 70° C. Stringent salt conditions will

25 ordinarily be less than about 500 mM, usually less than about 400 mM, more usually less than about 300 mM, typically less than about 200 mM, preferably less than about 100 mM, and more preferably less than about 80 mM, even down to less than about 20 mM. However, the

30 combination of parameters is much more important than the measure of any single parameter. See, e.g., Wetmur and Davidson (1968) J. Mol. Biol. 31:349-370, which is hereby incorporated herein by reference.

Alternatively, for sequence comparison, typically one

35 sequence acts as a reference sequence, to which test sequences are compared. When using a sequence comparison

algorithm, test and reference sequences are input into a computer, subsequence coordinates are designated, if necessary, and sequence algorithm program parameters are designated. The sequence comparison algorithm then
5 calculates the percent sequence identity for the test sequence(s) relative to the reference sequence, based on the designated program parameters.

Optical alignment of sequences for comparison can be conducted, e.g., by the local homology algorithm of Smith and Waterman (1981) Adv. Appl. Math. 2:482, by the
10 homology alignment algorithm of Needleman and Wunsch (1970) J. Mol. Biol. 48:443, by the search for similarity method of Pearson and Lipman (1988) Proc. Nat'l Acad. Sci. USA 85:2444, by computerized implementations of these
15 algorithms (GAP, BESTFIT, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group, 575 Science Dr., Madison, WI), or by visual inspection (see generally Ausubel et al., supra).

One example of a useful algorithm is PILEUP. PILEUP
20 creates a multiple sequence alignment from a group of related sequences using progressive, pairwise alignments to show relationship and percent sequence identity. It also plots a tree or dendrogram showing the clustering relationships used to create the alignment. PILEUP uses a
25 simplification of the progressive alignment method of Feng and Doolittle (1987) J. Mol. Evol. 35:351-360. The method used is similar to the method described by Higgins and Sharp (1989) CABIOS 5:151-153. The program can align up to 300 sequences, each of a maximum length of 5,000
30 nucleotides or amino acids. The multiple alignment procedure begins with the pairwise alignment of the two most similar sequences, producing a cluster of two aligned sequences. This cluster is then aligned to the next most related sequence or cluster of aligned sequences. Two
35 clusters of sequences are aligned by a simple extension of the pairwise alignment of two individual sequences. The

final alignment is achieved by a series of progressive, pairwise alignments. The program is run by designating specific sequences and their amino acid or nucleotide coordinates for regions of sequence, comparison and by designating the program parameters. For example, a reference sequence can be compared to other test sequences to determine the percent sequence identity relationship using the following parameters: default gap weight (3.00), default gap length weight (0.10), and weighted end gaps.

Another example of algorithm that is suitable for determining percent sequence identity and sequence similarity is the BLAST algorithm, which is described Altschul, et al. (1990) J. Mol. Biol. 215:403-410. Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information (<http://www.ncbi.nlm.nih.gov/>). This algorithm involves first identifying high scoring sequence pairs (HSPs) by identifying short words of length W in the query sequence, which either match or satisfy some positive-valued threshold score T when aligned with a word of the same length in a database sequence. T is referred to as the neighborhood word score threshold (Altschul, et al., supra). These initial neighborhood word hits act as seeds for initiating searches to find longer HSPs containing them. The word hits are then extended in both directions along each sequence for as far as the cumulative alignment score can be increased. Extension of the word hits in each direction are halted when: the cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments; or the end of either sequence is reached. The BLAST algorithm parameters W, T, and X determine the sensitivity and speed of the alignment. The BLAST program uses as defaults a wordlength (W) of 11, the BLOSUM62 scoring matrix (see Henikoff and Henikoff (1989)

Proc. Nat'l Acad. Sci. USA 89:10915) alignments (B) of 50, expectation (E) of 10, M=5, N=4, and a comparison of both strands.

In addition to calculating percent sequence identity, the BLAST algorithm also performs a statistical analysis of the similarity between two sequences (see, e.g., Karlin and Altschul (1993) Proc. Nat'l Acad. Sci. USA 90:5873-5787). One measure of similarity provided by the BLAST algorithm is the smallest sum probability (P(N)), which provides an indication of the probability by which a match between two nucleotide or amino acid sequences would occur by chance. For example, a nucleic acid is considered similar to a reference sequence if the smallest sum probability in a comparison of the test nucleic acid to the reference nucleic acid is less than about 0.1, more preferably less than about 0.01, and most preferably less than about 0.001.

A further indication that two nucleic acid sequences of polypeptides are substantially identical is that the polypeptide encoded by the first nucleic acid is immunologically cross reactive with the polypeptide encoded by the second nucleic acid, as described below. Thus, a polypeptide is typically substantially identical to a second polypeptide, e.g., where the two peptides differ only by conservative substitutions. Another indication that two nucleic acid sequences are substantially identical is that the two molecules hybridize to each other under stringent conditions, as described below.

The isolated DNA can be readily modified by nucleotide substitutions, nucleotide deletions, nucleotide insertions, and inversions of nucleotide stretches. These modifications result in novel DNA sequences which encode this protein or its derivatives. These modified sequences can be used to produce mutant proteins (muteins) or to enhance the expression of variant species. Enhanced

expression may involve gene amplification, increased transcription, increased translation, and other mechanisms. Such mutant DTLR-like derivatives include predetermined or site-specific mutations of the protein or
5 its fragments, including silent mutations using genetic code degeneracy. "Mutant DTLR" as used herein encompasses a polypeptide otherwise falling within the homology definition of the DTLR as set forth above, but having an amino acid sequence which differs from that of other DTLR-
10 like proteins as found in nature, whether by way of deletion, substitution, or insertion. In particular, "site specific mutant DTLR" encompasses a protein having substantial homology with a protein of Tables 2-10, and typically shares most of the biological activities or
15 effects of the forms disclosed herein.

Although site specific mutation sites are predetermined, mutants need not be site specific. Mammalian DTLR mutagenesis can be achieved by making amino acid insertions or deletions in the gene, coupled with
20 expression. Substitutions, deletions, insertions, or any combinations may be generated to arrive at a final construct. Insertions include amino- or carboxy- terminal fusions. Random mutagenesis can be conducted at a target codon and the expressed mammalian DTLR mutants can then be
25 screened for the desired activity. Methods for making substitution mutations at predetermined sites in DNA having a known sequence are well known in the art, e.g., by M13 primer mutagenesis. See also Sambrook, et al. (1989) and Ausubel, et al. (1987 and periodic
30 Supplements).

The mutations in the DNA normally should not place coding sequences out of reading frames and preferably will not create complementary regions that could hybridize to produce secondary mRNA structure such as loops or
35 hairpins.

The phosphoramidite method described by Beaucage and Carruthers (1981) Tetra. Letts. 22:1859-1862, will produce suitable synthetic DNA fragments. A double stranded fragment will often be obtained either by synthesizing the complementary strand and annealing the strand together under appropriate conditions or by adding the complementary strand using DNA polymerase with an appropriate primer sequence.

Polymerase chain reaction (PCR) techniques can often be applied in mutagenesis. Alternatively, mutagenesis primers are commonly used methods for generating defined mutations at predetermined sites. See, e.g., Innis, et al. (eds. 1990) PCR Protocols: A Guide to Methods and Applications Academic Press, San Diego, CA; and Dieffenbach and Dveksler (eds. 1995) PCR Primer: A Laboratory Manual Cold Spring Harbor Press, CSH, NY.

IV. Proteins, Peptides

As described above, the present invention encompasses primate DTLR2-10, e.g., whose sequences are disclosed in Tables 2-10, and described above. Allelic and other variants are also contemplated, including, e.g., fusion proteins combining portions of such sequences with others, including epitope tags and functional domains.

The present invention also provides recombinant proteins, e.g., heterologous fusion proteins using segments from these rodent proteins. A heterologous fusion protein is a fusion of proteins or segments which are naturally not normally fused in the same manner. Thus, the fusion product of a DTLR with an IL-1 receptor is a continuous protein molecule having sequences fused in a typical peptide linkage, typically made as a single translation product and exhibiting properties, e.g., sequence or antigenicity, derived from each source peptide. A similar concept applies to heterologous nucleic acid sequences.

In addition, new constructs may be made from combining similar functional or structural domains from other related proteins, e.g., IL-1 receptors or other DTLRs, including species variants. For example, ligand-binding or other segments may be "swapped" between different new fusion polypeptides or fragments. See, e.g., Cunningham, et al. (1989) Science 243:1330-1336; and O'Dowd, et al. (1988) J. Biol. Chem. 263:15985-15992, each of which is incorporated herein by reference. Thus, new chimeric polypeptides exhibiting new combinations of specificities will result from the functional linkage of receptor-binding specificities. For example, the ligand binding domains from other related receptor molecules may be added or substituted for other domains of this or related proteins. The resulting protein will often have hybrid function and properties. For example, a fusion protein may include a targeting domain which may serve to provide sequestering of the fusion protein to a particular subcellular organelle.

Candidate fusion partners and sequences can be selected from various sequence data bases, e.g., GenBank, c/o IntelliGenetics, Mountain View, CA; and BCG, University of Wisconsin Biotechnology Computing Group, Madison, WI, which are each incorporated herein by reference.

The present invention particularly provides muteins which bind Toll ligands, and/or which are affected in signal transduction. Structural alignment of human DTLR1-10 with other members of the IL-1 family show conserved features/residues. See, e.g., Figure 3A. Alignment of the human DTLR sequences with other members of the IL-1 family indicates various structural and functionally shared features. See also, Bazan, et al. (1996) Nature 379:591; Lodi, et al. (1994) Science 263:1762-1766; Sayle and Milner-White (1995) TIBS 20:374-376; and Gronenberg, et al. (1991) Protein Engineering 4:263-269.

The IL-1 α and IL-1 β ligands bind an IL-1 receptor type I as the primary receptor and this complex then forms a high affinity receptor complex with the IL-1 receptor type III. Such receptor subunits are probably shared with
5 the new IL-1 family members.

Similar variations in other species counterparts of DTLR2-10 sequences, e.g., in the corresponding regions, should provide similar interactions with ligand or substrate. Substitutions with either mouse sequences or
10 human sequences are particularly preferred. Conversely, conservative substitutions away from the ligand binding interaction regions will probably preserve most signaling activities.

"Derivatives" of the primate DTLR2-10 include amino
15 acid sequence mutants, glycosylation variants, metabolic derivatives and covalent or aggregative conjugates with other chemical moieties. Covalent derivatives can be prepared by linkage of functionalities to groups which are found in the DTLR amino acid side chains or at the N- or
20 C- termini, e.g., by means which are well known in the art. These derivatives can include, without limitation, aliphatic esters or amides of the carboxyl terminus, or of residues containing carboxyl side chains, O-acyl
derivatives of hydroxyl group-containing residues, and
25 N-acyl derivatives of the amino terminal amino acid or amino-group containing residues, e.g., lysine or arginine. Acyl groups are selected from the group of alkyl-moieties including C3 to C18 normal alkyl, thereby forming alkanoyl
aroyl species.

30 In particular, glycosylation alterations are included, e.g., made by modifying the glycosylation patterns of a polypeptide during its synthesis and processing, or in further processing steps. Particularly preferred means for accomplishing this are by exposing the
35 polypeptide to glycosylating enzymes derived from cells which normally provide such processing, e.g., mammalian

glycosylation enzymes. Deglycosylation enzymes are also contemplated. Also embraced are versions of the same primary amino acid sequence which have other minor modifications, including phosphorylated amino acid residues, e.g., phosphotyrosine, phosphoserine, or phosphothreonine.

A major group of derivatives are covalent conjugates of the receptors or fragments thereof with other proteins of polypeptides. These derivatives can be synthesized in recombinant culture such as N- or C-terminal fusions or by the use of agents known in the art for their usefulness in cross-linking proteins through reactive side groups. Preferred derivatization sites with cross-linking agents are at free amino groups, carbohydrate moieties, and cysteine residues.

Fusion polypeptides between the receptors and other homologous or heterologous proteins are also provided. Homologous polypeptides may be fusions between different receptors, resulting in, for instance, a hybrid protein exhibiting binding specificity for multiple different Toll ligands, or a receptor which may have broadened or weakened specificity of substrate effect. Likewise, heterologous fusions may be constructed which would exhibit a combination of properties or activities of the derivative proteins. Typical examples are fusions of a reporter polypeptide, e.g., luciferase, with a segment or domain of a receptor, e.g., a ligand-binding segment, so that the presence or location of a desired ligand may be easily determined. See, e.g., Dull, et al., U.S. Patent No. 4,859,609, which is hereby incorporated herein by reference. Other gene fusion partners include glutathione-S-transferase (GST), bacterial β -galactosidase, trpE, Protein A, β -lactamase, alpha amylase, alcohol dehydrogenase, and yeast alpha mating factor. See, e.g., Godowski, et al. (1988) Science 241:812-816.

The phosphoramidite method described by Beaucage and Carruthers (1981) Tetra. Letts. 22:1859-1862, will produce suitable synthetic DNA fragments. A double stranded fragment will often be obtained either by synthesizing the complementary strand and annealing the strand together under appropriate conditions or by adding the complementary strand using DNA polymerase with an appropriate primer sequence.

Such polypeptides may also have amino acid residues which have been chemically modified by phosphorylation, sulfonation, biotinylation, or the addition or removal of other moieties, particularly those which have molecular shapes similar to phosphate groups. In some embodiments, the modifications will be useful labeling reagents, or serve as purification targets, e.g., affinity ligands.

Fusion proteins will typically be made by either recombinant nucleic acid methods or by synthetic polypeptide methods. Techniques for nucleic acid manipulation and expression are described generally, for example, in Sambrook, et al. (1989) Molecular Cloning: A Laboratory Manual (2d ed.), Vols. 1-3, Cold Spring Harbor Laboratory, and Ausubel, et al. (eds. 1987 and periodic supplements) Current Protocols in Molecular Biology, Greene/Wiley, New York, which are each incorporated herein by reference. Techniques for synthesis of polypeptides are described, for example, in Merrifield (1963) J. Amer. Chem. Soc. 85:2149-2156; Merrifield (1986) Science 232: 341-347; and Atherton, et al. (1989) Solid Phase Peptide Synthesis: A Practical Approach, IRL Press, Oxford; each of which is incorporated herein by reference. See also Dawson, et al. (1994) Science 266:776-779 for methods to make larger polypeptides.

This invention also contemplates the use of derivatives of a DTLR2-10 other than variations in amino acid sequence or glycosylation. Such derivatives may involve covalent or aggregative association with chemical

moieties. These derivatives generally fall into three classes: (1) salts, (2) side chain and terminal residue covalent modifications, and (3) adsorption complexes, for example with cell membranes. Such covalent or aggregative derivatives are useful as immunogens, as reagents in immunoassays, or in purification methods such as for affinity purification of a receptor or other binding molecule, e.g., an antibody. For example, a Toll ligand can be immobilized by covalent bonding to a solid support such as cyanogen bromide-activated Sepharose, by methods which are well known in the art, or adsorbed onto polyolefin surfaces, with or without glutaraldehyde cross-linking, for use in the assay or purification of a DTLR receptor, antibodies, or other similar molecules. The ligand can also be labeled with a detectable group, for example radioiodinated by the chloramine T procedure, covalently bound to rare earth chelates, or conjugated to another fluorescent moiety for use in diagnostic assays.

A DTLR of this invention can be used as an immunogen for the production of antisera or antibodies specific, e.g., capable of distinguishing between other IL-1 receptor family members, for the DTLR or various fragments thereof. The purified DTLR can be used to screen monoclonal antibodies or antigen-binding fragments prepared by immunization with various forms of impure preparations containing the protein. In particular, the term "antibodies" also encompasses antigen binding fragments of natural antibodies, e.g., Fab, Fab2, Fv, etc. The purified DTLR can also be used as a reagent to detect antibodies generated in response to the presence of elevated levels of expression, or immunological disorders which lead to antibody production to the endogenous receptor. Additionally, DTLR fragments may also serve as immunogens to produce the antibodies of the present invention, as described immediately below. For example, this invention contemplates antibodies having binding

affinity to or being raised against the amino acid sequences shown in Tables 2-10, fragments thereof, or various homologous peptides. In particular, this invention contemplates antibodies having binding affinity
5 to, or having been raised against, specific fragments which are predicted to be, or actually are, exposed at the exterior protein surface of the native DTLR.

The blocking of physiological response to the receptor ligands may result from the inhibition of binding
10 of the ligand to the receptor, likely through competitive inhibition. Thus, in vitro assays of the present invention will often use antibodies or antigen binding segments of these antibodies, or fragments attached to solid phase substrates. These assays will also allow for
15 the diagnostic determination of the effects of either ligand binding region mutations and modifications, or other mutations and modifications, e.g., which affect signaling or enzymatic function.

This invention also contemplates the use of
20 competitive drug screening assays, e.g., where neutralizing antibodies to the receptor or fragments compete with a test compound for binding to a ligand or other antibody. In this manner, the neutralizing antibodies or fragments can be used to detect the presence
25 of a polypeptide which shares one or more binding sites to a receptor and can also be used to occupy binding sites on a receptor that might otherwise bind a ligand.

V. Making Nucleic Acids and Protein

30 DNA which encodes the protein or fragments thereof can be obtained by chemical synthesis, screening cDNA libraries, or by screening genomic libraries prepared from a wide variety of cell lines or tissue samples. Natural sequences can be isolated using standard methods and the
35 sequences provided herein, e.g., in Tables 2-10. Other species counterparts can be identified by hybridization

techniques, or by various PCR techniques, combined with or by searching in sequence databases, e.g., GenBank.

This DNA can be expressed in a wide variety of host cells for the synthesis of a full-length receptor or fragments which can in turn, for example, be used to generate polyclonal or monoclonal antibodies; for binding studies; for construction and expression of modified ligand binding or kinase/phosphatase domains; and for structure/function studies. Variants or fragments can be expressed in host cells that are transformed or transfected with appropriate expression vectors. These molecules can be substantially free of protein or cellular contaminants, other than those derived from the recombinant host, and therefore are particularly useful in pharmaceutical compositions when combined with a pharmaceutically acceptable carrier and/or diluent. The protein, or portions thereof, may be expressed as fusions with other proteins.

Expression vectors are typically self-replicating DNA or RNA constructs containing the desired receptor gene or its fragments, usually operably linked to suitable genetic control elements that are recognized in a suitable host cell. These control elements are capable of effecting expression within a suitable host. The specific type of control elements necessary to effect expression will depend upon the eventual host cell used. Generally, the genetic control elements can include a prokaryotic promoter system or a eukaryotic promoter expression control system, and typically include a transcriptional promoter, an optional operator to control the onset of transcription, transcription enhancers to elevate the level of mRNA expression, a sequence that encodes a suitable ribosome binding site, and sequences that terminate transcription and translation. Expression vectors also usually contain an origin of replication that

allows the vector to replicate independently of the host cell.

The vectors of this invention include those which contain DNA which encodes a protein, as described, or a
5 fragment thereof encoding a biologically active equivalent polypeptide. The DNA can be under the control of a viral promoter and can encode a selection marker. This invention further contemplates use of such expression
10 vectors which are capable of expressing eukaryotic cDNA coding for such a protein in a prokaryotic or eukaryotic host, where the vector is compatible with the host and where the eukaryotic cDNA coding for the receptor is inserted into the vector such that growth of the host containing the vector expresses the cDNA in question.
15 Usually, expression vectors are designed for stable replication in their host cells or for amplification to greatly increase the total number of copies of the desirable gene per cell. It is not always necessary to require that an expression vector replicate in a host
20 cell, e.g., it is possible to effect transient expression of the protein or its fragments in various hosts using vectors that do not contain a replication origin that is recognized by the host cell. It is also possible to use vectors that cause integration of the protein encoding
25 portion or its fragments into the host DNA by recombination.

Vectors, as used herein, comprise plasmids, viruses, bacteriophage, integratable DNA fragments, and other
30 vehicles which enable the integration of DNA fragments into the genome of the host. Expression vectors are specialized vectors which contain genetic control elements that effect expression of operably linked genes. Plasmids are the most commonly used form of vector but all other forms of vectors which serve an equivalent function and
35 which are, or become, known in the art are suitable for use herein. See, e.g., Pouwels, et al. (1985 and

Supplements) Cloning Vectors: A Laboratory Manual, Elsevier, N.Y., and Rodriguez, et al. (eds.) Vectors: A Survey of Molecular Cloning Vectors and Their Uses, Butterworth, Boston, 1988, which are incorporated herein
5 by reference.

Transformed cells are cells, preferably mammalian, that have been transformed or transfected with receptor vectors constructed using recombinant DNA techniques. Transformed host cells usually express the desired protein
10 or its fragments, but for purposes of cloning, amplifying, and manipulating its DNA, do not need to express the subject protein. This invention further contemplates culturing transformed cells in a nutrient medium, thus permitting the receptor to accumulate in the cell
15 membrane. The protein can be recovered, either from the culture or, in certain instances, from the culture medium.

For purposes of this invention, nucleic sequences are operably linked when they are functionally related to each other. For example, DNA for a presequence or secretory
20 leader is operably linked to a polypeptide if it is expressed as a preprotein or participates in directing the polypeptide to the cell membrane or in secretion of the polypeptide. A promoter is operably linked to a coding sequence if it controls the transcription of the
25 polypeptide; a ribosome binding site is operably linked to a coding sequence if it is positioned to permit translation. Usually, operably linked means contiguous and in reading frame, however, certain genetic elements such as repressor genes are not contiguously linked but still
30 bind to operator sequences that in turn control expression.

Suitable host cells include prokaryotes, lower eukaryotes, and higher eukaryotes. Prokaryotes include both gram negative and gram positive organisms, e.g., E. coli and B. subtilis. Lower eukaryotes include yeasts,
35 e.g., S. cerevisiae and Pichia, and species of the genus

Dictyostelium. Higher eukaryotes include established tissue culture cell lines from animal cells, both of non-mammalian origin, e.g., insect cells, and birds, and of mammalian origin, e.g., human, primates, and rodents.

5 Prokaryotic host-vector systems include a wide variety of vectors for many different species. As used herein, E. coli and its vectors will be used generically to include equivalent vectors used in other prokaryotes. A representative vector for amplifying DNA is pBR322 or
10 many of its derivatives. Vectors that can be used to express the receptor or its fragments include, but are not limited to, such vectors as those containing the lac promoter (pUC-series); trp promoter (pBR322-trp); Ipp promoter (the pIN-series); lambda-pP or pR promoters
15 (pOTS); or hybrid promoters such as ptac (pDR540). See Brosius, et al. (1988) "Expression Vectors Employing Lambda-, trp-, lac-, and Ipp-derived Promoters", in Vectors: A Survey of Molecular Cloning Vectors and Their Uses, (eds. Rodriguez and Denhardt), Butterworth, Boston,
20 Chapter 10, pp. 205-236, which is incorporated herein by reference.

Lower eukaryotes, e.g., yeasts and Dictyostelium, may be transformed with DTLR sequence containing vectors. For purposes of this invention, the most common lower
25 eukaryotic host is the baker's yeast, Saccharomyces cerevisiae. It will be used to generically represent lower eukaryotes although a number of other strains and species are also available. Yeast vectors typically consist of a replication origin (unless of the integrating
30 type), a selection gene, a promoter, DNA encoding the receptor or its fragments, and sequences for translation termination, polyadenylation, and transcription termination. Suitable expression vectors for yeast include such constitutive promoters as 3-phosphoglycerate
35 kinase and various other glycolytic enzyme gene promoters or such inducible promoters as the alcohol dehydrogenase 2

promoter or metallothionine promoter. Suitable vectors include derivatives of the following types:
self-replicating low copy number (such as the YRp-series),
self-replicating high copy number (such as the
5 YEp-series); integrating types (such as the YIp-series),
or mini-chromosomes (such as the YCp-series).

Higher eukaryotic tissue culture cells are normally the preferred host cells for expression of the functionally active interleukin protein. In principle,
10 any higher eukaryotic tissue culture cell line is workable, e.g., insect baculovirus expression systems, whether from an invertebrate or vertebrate source. However, mammalian cells are preferred. Transformation or transfection and propagation of such cells has become a
15 routine procedure. Examples of useful cell lines include HeLa cells, Chinese hamster ovary (CHO) cell lines, baby rat kidney (BRK) cell lines, insect cell lines, bird cell lines, and monkey (COS) cell lines. Expression vectors for such cell lines usually include an origin of
20 replication, a promoter, a translation initiation site, RNA splice sites (if genomic DNA is used), a polyadenylation site, and a transcription termination site. These vectors also usually contain a selection gene or amplification gene. Suitable expression vectors may be
25 plasmids, viruses, or retroviruses carrying promoters derived, e.g., from such sources as from adenovirus, SV40, parvoviruses, vaccinia virus, or cytomegalovirus. Representative examples of suitable expression vectors include pCDNA1; pCD, see Okayama, et al. (1985) Mol. Cell
30 Biol. 5:1136-1142; pMC1neo PolyA, see Thomas, et al. (1987) Cell 51:503-512; and a baculovirus vector such as pAC 373 or pAC 610.

For secreted proteins, an open reading frame usually encodes a polypeptide that consists of a mature or
35 secreted product covalently linked at its N-terminus to a signal peptide. The signal peptide is cleaved prior to

secretion of the mature, or active, polypeptide. The cleavage site can be predicted with a high degree of accuracy from empirical rules, e.g., von-Heijne (1986) Nucleic Acids Research 14:4683-4690, and the precise amino acid composition of the signal peptide does not appear to be critical to its function, e.g., Randall, et al. (1989) Science 243:1156-1159; Kaiser, et al. (1987) Science 235:312-317.

It will often be desired to express these polypeptides in a system which provides a specific or defined glycosylation pattern. In this case, the usual pattern will be that provided naturally by the expression system. However, the pattern will be modifiable by exposing the polypeptide, e.g., an unglycosylated form, to appropriate glycosylating proteins introduced into a heterologous expression system. For example, the receptor gene may be co-transformed with one or more genes encoding mammalian or other glycosylating enzymes. Using this approach, certain mammalian glycosylation patterns will be achievable in prokaryote or other cells.

The source of DTLR can be a eukaryotic or prokaryotic host expressing recombinant DTLR, such as is described above. The source can also be a cell line such as mouse Swiss 3T3 fibroblasts, but other mammalian cell lines are also contemplated by this invention, with the preferred cell line being from the human species.

Now that the sequences are known, the primate DTLRs, fragments, or derivatives thereof can be prepared by conventional processes for synthesizing peptides. These include processes such as are described in Stewart and Young (1984) Solid Phase Peptide Synthesis, Pierce Chemical Co., Rockford, IL; Bodanszky and Bodanszky (1984) The Practice of Peptide Synthesis, Springer-Verlag, New York; and Bodanszky (1984) The Principles of Peptide Synthesis, Springer-Verlag, New York; all of each which are incorporated herein by reference. For example, an

azide process, an acid chloride process, an acid anhydride process, a mixed anhydride process, an active ester process (e.g., p-nitrophenyl ester, N-hydroxysuccinimide ester, or cyanomethyl ester), a carbodiimidazole process, 5 an oxidative-reductive process, or a dicyclohexylcarbodiimide (DCCD)/additive process can be used. Solid phase and solution phase syntheses are both applicable to the foregoing processes. Similar techniques can be used with partial DTLR sequences.

10 The DTLR proteins, fragments, or derivatives are suitably prepared in accordance with the above processes as typically employed in peptide synthesis, generally either by a so-called stepwise process which comprises condensing an amino acid to the terminal amino acid, one 15 by one in sequence, or by coupling peptide fragments to the terminal amino acid. Amino groups that are not being used in the coupling reaction typically must be protected to prevent coupling at an incorrect location.

If a solid phase synthesis is adopted, the C-terminal 20 amino acid is bound to an insoluble carrier or support through its carboxyl group. The insoluble carrier is not particularly limited as long as it has a binding capability to a reactive carboxyl group. Examples of such insoluble carriers include halomethyl resins, such as 25 chloromethyl resin or bromomethyl resin, hydroxymethyl resins, phenol resins, tert-alkyloxycarbonylhydrazidated resins, and the like.

An amino group-protected amino acid is bound in sequence through condensation of its activated carboxyl 30 group and the reactive amino group of the previously formed peptide or chain, to synthesize the peptide step by step. After synthesizing the complete sequence, the peptide is split off from the insoluble carrier to produce the peptide. This solid-phase approach is generally 35 described by Merrifield, et al. (1963) in J. Am. Chem.

Soc. 85:2149-2156, which is incorporated herein by reference.

The prepared protein and fragments thereof can be isolated and purified from the reaction mixture by means of peptide separation, for example, by extraction, precipitation, electrophoresis, various forms of chromatography, and the like. The receptors of this invention can be obtained in varying degrees of purity depending upon desired uses. Purification can be accomplished by use of the protein purification techniques disclosed herein, see below, or by the use of the antibodies herein described in methods of immunoabsorbant affinity chromatography. This immunoabsorbant affinity chromatography is carried out by first linking the antibodies to a solid support and then contacting the linked antibodies with solubilized lysates of appropriate cells, lysates of other cells expressing the receptor, or lysates or supernatants of cells producing the protein as a result of DNA techniques, see below.

Generally, the purified protein will be at least about 40% pure, ordinarily at least about 50% pure, usually at least about 60% pure, typically at least about 70% pure, more typically at least about 80% pure, preferable at least about 90% pure and more preferably at least about 95% pure, and in particular embodiments, 97%-99% or more. Purity will usually be on a weight basis, but can also be on a molar basis. Different assays will be applied as appropriate.

30 VI. Antibodies

Antibodies can be raised to the various mammalian, e.g., primate DTLR proteins and fragments thereof, both in naturally occurring native forms and in their recombinant forms, the difference being that antibodies to the active receptor are more likely to recognize epitopes which are only present in the native conformations. Denatured

antigen detection can also be useful in, e.g., Western analysis. Anti-idiotypic antibodies are also contemplated, which would be useful as agonists or antagonists of a natural receptor or an antibody.

5 Preferred antibodies will exhibit properties of both affinity and selectivity. High affinity is generally preferred, while selectivity will allow distinction between various embodiment subsets. In particular, it will be desirable to possess antibody preparations
10 characterized to bind, e.g., various specific combinations of related members while not binding others. Such various combinatorial subsets are specifically enabled, e.g., these reagents may be generated or selected using standard methods of immunoaffinity, selection, etc.

15 Antibodies, including binding fragments and single chain versions, against predetermined fragments of the protein can be raised by immunization of animals with conjugates of the fragments with immunogenic proteins. Monoclonal antibodies are prepared from cells secreting
20 the desired antibody. These antibodies can be screened for binding to normal or defective protein, or screened for agonistic or antagonistic activity. These monoclonal antibodies will usually bind with at least a K_D of about 1 mM, more usually at least about 300 μ M, typically at least
25 about 100 μ M, more typically at least about 30 μ M, preferably at least about 10 μ M, and more preferably at least about 3 μ M or better.

The antibodies, including antigen binding fragments, of this invention can have significant diagnostic or
30 therapeutic value. They can be potent antagonists that bind to the receptor and inhibit binding to ligand or inhibit the ability of the receptor to elicit a biological response, e.g., act on its substrate. They also can be useful as non-neutralizing antibodies and can be coupled
35 to toxins or radionuclides to bind producing cells, or cells localized to the source of the interleukin.

Further, these antibodies can be conjugated to drugs or other therapeutic agents, either directly or indirectly by means of a linker.

The antibodies of this invention can also be useful
5 in diagnostic applications. As capture or non-neutralizing antibodies, they might bind to the receptor without inhibiting ligand or substrate binding. As neutralizing antibodies, they can be useful in competitive binding assays. They will also be useful in
10 detecting or quantifying ligand. They may be used as reagents for Western blot analysis, or for immunoprecipitation or immunopurification of the respective protein.

Protein fragments may be joined to other materials,
15 particularly polypeptides, as fused or covalently joined polypeptides to be used as immunogens. Mammalian DTLR and its fragments may be fused or covalently linked to a variety of immunogens, such as keyhole limpet hemocyanin, bovine serum albumin, tetanus toxoid, etc. See
20 Microbiology, Hoeber Medical Division, Harper and Row, 1969; Landsteiner (1962) Specificity of Serological Reactions, Dover Publications, New York; and Williams, et al. (1967) Methods in Immunology and Immunochemistry, Vol. 1, Academic Press, New York; each of which are
25 incorporated herein by reference, for descriptions of methods of preparing polyclonal antisera. A typical method involves hyperimmunization of an animal with an antigen. The blood of the animal is then collected shortly after the repeated immunizations and the gamma
30 globulin is isolated.

In some instances, it is desirable to prepare monoclonal antibodies from various mammalian hosts, such as mice, rodents, primates, humans, etc. Description of techniques for preparing such monoclonal antibodies may be
35 found in, e.g., Stites, et al. (eds.) Basic and Clinical Immunology (4th ed.), Lange Medical Publications, Los

Altos, CA, and references cited therein; Harlow and Lane (1988) Antibodies: A Laboratory Manual, CSH Press; Goding (1986) Monoclonal Antibodies: Principles and Practice (2d ed) Academic Press, New York; and particularly in Kohler and Milstein (1975) in Nature 256: 495-497, which discusses one method of generating monoclonal antibodies. Each of these references is incorporated herein by reference. Summarized briefly, this method involves injecting an animal with an immunogen. The animal is then sacrificed and cells taken from its spleen, which are then fused with myeloma cells. The result is a hybrid cell or "hybridoma" that is capable of reproducing in vitro. The population of hybridomas is then screened to isolate individual clones, each of which secrete a single antibody species to the immunogen. In this manner, the individual antibody species obtained are the products of immortalized and cloned single B cells from the immune animal generated in response to a specific site recognized on the immunogenic substance.

Other suitable techniques involve in vitro exposure of lymphocytes to the antigenic polypeptides or alternatively to selection of libraries of antibodies in phage or similar vectors. See, Huse, et al. (1989) "Generation of a Large Combinatorial Library of the Immunoglobulin Repertoire in Phage Lambda," Science 246:1275-1281; and Ward, et al. (1989) Nature 341:544-546, each of which is hereby incorporated herein by reference. The polypeptides and antibodies of the present invention may be used with or without modification, including chimeric or humanized antibodies. Frequently, the polypeptides and antibodies will be labeled by joining, either covalently or non-covalently, a substance which provides for a detectable signal. A wide variety of labels and conjugation techniques are known and are reported extensively in both the scientific and patent literature. Suitable labels include radionuclides,

enzymes, substrates, cofactors, inhibitors, fluorescent moieties, chemiluminescent moieties, magnetic particles, and the like. Patents, teaching the use of such labels include U.S. Patent Nos. 3,817,837; 3,850,752; 3,939,350; 5 3,996,345; 4,277,437; 4,275,149; and 4,366,241. Also, recombinant or chimeric immunoglobulins may be produced, see Cabilly, U.S. Patent No. 4,816,567; or made in transgenic mice, see Mendez, et al. (1997) Nature Genetics 15:146-156. These references are incorporated herein by
10 reference.

The antibodies of this invention can also be used for affinity chromatography in isolating the DTLRs. Columns can be prepared where the antibodies are linked to a solid support, e.g., particles, such as agarose, Sephadex, or
15 the like, where a cell lysate may be passed through the column, the column washed, followed by increasing concentrations of a mild denaturant, whereby the purified protein will be released. The protein may be used to purify antibody.

20 The antibodies may also be used to screen expression libraries for particular expression products. Usually the antibodies used in such a procedure will be labeled with a moiety allowing easy detection of presence of antigen by antibody binding.

25 Antibodies raised against a DTLR will also be used to raise anti-idiotypic antibodies. These will be useful in detecting or diagnosing various immunological conditions related to expression of the protein or cells which express the protein. They also will be useful as agonists
30 or antagonists of the ligand, which may be competitive inhibitors or substitutes for naturally occurring ligands.

A DTLR protein that specifically binds to or that is specifically immunoreactive with an antibody generated against a defined immunogen, such as an immunogen
35 consisting of the amino acid sequence of SEQ ID NO: 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, or 24, is typically

determined in an immunoassay. The immunoassay typically uses a polyclonal antiserum which was raised, e.g., to a protein of SEQ ID NO: 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, or 24. This antiserum is selected to have low crossreactivity against other IL-1R family members, e.g., DTLR1, preferably from the same species, and any such crossreactivity is removed by immunoabsorption prior to use in the immunoassay.

In order to produce antisera for use in an immunoassay, the protein of SEQ ID NO: 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, or 24, or a combination thereof, is isolated as described herein. For example, recombinant protein may be produced in a mammalian cell line. An appropriate host, e.g., an inbred strain of mice such as Balb/c, is immunized with the selected protein, typically using a standard adjuvant, such as Freund's adjuvant, and a standard mouse immunization protocol (see Harlow and Lane, supra). Alternatively, a synthetic peptide derived from the sequences disclosed herein and conjugated to a carrier protein can be used as an immunogen. Polyclonal sera are collected and titered against the immunogen protein in an immunoassay, e.g., a solid phase immunoassay with the immunogen immobilized on a solid support. Polyclonal antisera with a titer of 10^4 or greater are selected and tested for their cross reactivity against other IL-1R family members, e.g., mouse DTLRs or human DTLR1, using a competitive binding immunoassay such as the one described in Harlow and Lane, supra, at pages 570-573. Preferably at least two DTLR family members are used in this determination in conjunction with either or some of the human DTLR2-10. These IL-1R family members can be produced as recombinant proteins and isolated using standard molecular biology and protein chemistry techniques as described herein.

Immunoassays in the competitive binding format can be used for the crossreactivity determinations. For example,

the proteins of SEQ ID NO: 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, and/or 24, or various fragments thereof, can be immobilized to a solid support. Proteins added to the assay compete with the binding of the antisera to the immobilized antigen. The ability of the above proteins to compete with the binding of the antisera to the immobilized protein is compared to the protein of SEQ ID NO: 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, and/or 24. The percent crossreactivity for the above proteins is calculated, using standard calculations. Those antisera with less than 10% crossreactivity with each of the proteins listed above are selected and pooled. The cross-reacting antibodies are then removed from the pooled antisera by immunoabsorption with the above-listed proteins.

The immunoabsorbed and pooled antisera are then used in a competitive binding immunoassay as described above to compare a second protein to the immunogen protein (e.g., the IL-1R like protein of SEQ ID NO: 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, and/or 24). In order to make this comparison, the two proteins are each assayed at a wide range of concentrations and the amount of each protein required to inhibit 50% of the binding of the antisera to the immobilized protein is determined. If the amount of the second protein required is less than twice the amount of the protein of the selected protein or proteins that is required, then the second protein is said to specifically bind to an antibody generated to the immunogen.

It is understood that these DTLR proteins are members of a family of homologous proteins that comprise at least 10 so far identified genes. For a particular gene product, such as the DTLR2-10, the term refers not only to the amino acid sequences disclosed herein, but also to other proteins that are allelic, non-allelic or species variants. It is also understood that the terms include nonnatural mutations introduced by deliberate mutation

using conventional recombinant technology such as single site mutation, or by excising short sections of DNA encoding the respective proteins, or by substituting new amino acids, or adding new amino acids. Such minor alterations must substantially maintain the immunoidentity of the original molecule and/or its biological activity. Thus, these alterations include proteins that are specifically immunoreactive with a designated naturally occurring IL-1R related protein, for example, the DTLR proteins shown in SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, or 24. The biological properties of the altered proteins can be determined by expressing the protein in an appropriate cell line and measuring the appropriate effect upon lymphocytes. Particular protein modifications considered minor would include conservative substitution of amino acids with similar chemical properties, as described above for the IL-1R family as a whole. By aligning a protein optimally with the protein of DTLR2-10 and by using the conventional immunoassays described herein to determine immunoidentity, one can determine the protein compositions of the invention.

VII. Kits and quantitation

Both naturally occurring and recombinant forms of the IL-1R like molecules of this invention are particularly useful in kits and assay methods. For example, these methods would also be applied to screening for binding activity, e.g., ligands for these proteins. Several methods of automating assays have been developed in recent years so as to permit screening of tens of thousands of compounds per year. See, e.g., a BIOMEK automated workstation, Beckman Instruments, Palo Alto, California, and Fodor, et al. (1991) Science 251:767-773, which is incorporated herein by reference. The latter describes means for testing binding by a plurality of defined polymers synthesized on a solid substrate. The

development of suitable assays to screen for a ligand or agonist/antagonist homologous proteins can be greatly facilitated by the availability of large amounts of purified, soluble DTLRs in an active state such as is
5 provided by this invention.

Purified DTLR can be coated directly onto plates for use in the aforementioned ligand screening techniques. However, non-neutralizing antibodies to these proteins can be used as capture antibodies to immobilize the respective
10 receptor on the solid phase, useful, e.g., in diagnostic uses.

This invention also contemplates use of DTLR2-10, fragments thereof, peptides, and their fusion products in a variety of diagnostic kits and methods for detecting the
15 presence of the protein or its ligand. Alternatively, or additionally, antibodies against the molecules may be incorporated into the kits and methods. Typically the kit will have a compartment containing either a defined DTLR peptide or gene segment or a reagent which recognizes one
20 or the other. Typically, recognition reagents, in the case of peptide, would be a receptor or antibody, or in the case of a gene segment, would usually be a hybridization probe.

A preferred kit for determining the concentration of, e.g., DTLR4, a sample would typically comprise a labeled
25 compound, e.g., ligand or antibody, having known binding affinity for DTLR4, a source of DTLR4 (naturally occurring or recombinant) as a positive control, and a means for separating the bound from free labeled compound, for
30 example a solid phase for immobilizing the DTLR4 in the test sample. Compartments containing reagents, and instructions, will normally be provided.

Antibodies, including antigen binding fragments, specific for mammalian DTLR or a peptide fragment, or
35 receptor fragments are useful in diagnostic applications to detect the presence of elevated levels of ligand and/or

its fragments. Diagnostic assays may be homogeneous (without a separation step between free reagent and antibody-antigen complex) or heterogeneous (with a separation step). Various commercial assays exist, such as radioimmunoassay (RIA), enzyme-linked immunosorbent assay (ELISA), enzyme immunoassay (EIA), enzyme-multiplied immunoassay technique (EMIT), substrate-labeled fluorescent immunoassay (SLFIA) and the like. For example, unlabeled antibodies can be employed by using a second antibody which is labeled and which recognizes the antibody to DTLR4 or to a particular fragment thereof. These assays have also been extensively discussed in the literature. See, e.g., Harlow and Lane (1988) Antibodies: A Laboratory Manual, CSH., and Coligan (ed. 1991 and periodic supplements) Current Protocols In Immunology Greene/Wiley, New York.

Anti-idiotypic antibodies may have similar use to serve as agonists or antagonists of DTLR4. These should be useful as therapeutic reagents under appropriate circumstances.

Frequently, the reagents for diagnostic assays are supplied in kits, so as to optimize the sensitivity of the assay. For the subject invention, depending upon the nature of the assay, the protocol, and the label, either labeled or unlabeled antibody, or labeled ligand is provided. This is usually in conjunction with other additives, such as buffers, stabilizers, materials necessary for signal production such as substrates for enzymes, and the like. Preferably, the kit will also contain instructions for proper use and disposal of the contents after use. Typically the kit has compartments for each useful reagent, and will contain instructions for proper use and disposal of reagents. Desirably, the reagents are provided as a dry lyophilized powder, where the reagents may be reconstituted in an aqueous medium

having appropriate concentrations for performing the assay.

The aforementioned constituents of the diagnostic assays may be used without modification or may be modified in a variety of ways. For example, labeling may be achieved by covalently or non-covalently joining a moiety which directly or indirectly provides a detectable signal. In any of these assays, a test compound, DTLR, or antibodies thereto can be labeled either directly or indirectly. Possibilities for direct labeling include label groups: radiolabels such as ^{125}I , enzymes (U.S. Pat. No. 3,645,090) such as peroxidase and alkaline phosphatase, and fluorescent labels (U.S. Pat. No. 3,940,475) capable of monitoring the change in fluorescence intensity, wavelength shift, or fluorescence polarization. Both of the patents are incorporated herein by reference. Possibilities for indirect labeling include biotinylation of one constituent followed by binding to avidin coupled to one of the above label groups.

There are also numerous methods of separating the bound from the free ligand, or alternatively the bound from the free test compound. The DTLR can be immobilized on various matrixes followed by washing. Suitable matrices include plastic such as an ELISA plate, filters, and beads. Methods of immobilizing the receptor to a matrix include, without limitation, direct adhesion to plastic, use of a capture antibody, chemical coupling, and biotin-avidin. The last step in this approach involves the precipitation of antibody/antigen complex by any of several methods including those utilizing, e.g., an organic solvent such as polyethylene glycol or a salt such as ammonium sulfate. Other suitable separation techniques include, without limitation, the fluorescein antibody magnetizable particle method described in Rattle, et al. (1984) Clin. Chem. 30(9):1457-1461, and the double antibody magnetic particle separation as described in U.S.

Pat. No. 4,659,678, each of which is incorporated herein by reference.

The methods for linking protein or fragments to various labels have been extensively reported in the literature and do not require detailed discussion here. Many of the techniques involve the use of activated carboxyl groups either through the use of carbodiimide or active esters to form peptide bonds, the formation of thioethers by reaction of a mercapto group with an activated halogen such as chloroacetyl, or an activated olefin such as maleimide, for linkage, or the like. Fusion proteins will also find use in these applications.

Another diagnostic aspect of this invention involves use of oligonucleotide or polynucleotide sequences taken from the sequence of a DTLR. These sequences can be used as probes for detecting levels of the respective DTLR in patients suspected of having an immunological disorder. The preparation of both RNA and DNA nucleotide sequences, the labeling of the sequences, and the preferred size of the sequences has received ample description and discussion in the literature. Normally an oligonucleotide probe should have at least about 14 nucleotides, usually at least about 18 nucleotides, and the polynucleotide probes may be up to several kilobases. Various labels may be employed, most commonly radionuclides, particularly ^{32}P . However, other techniques may also be employed, such as using biotin modified nucleotides for introduction into a polynucleotide. The biotin then serves as the site for binding to avidin or antibodies, which may be labeled with a wide variety of labels, such as radionuclides, fluorescers, enzymes, or the like. Alternatively, antibodies may be employed which can recognize specific duplexes, including DNA duplexes, RNA duplexes, DNA-RNA hybrid duplexes, or DNA-protein duplexes. The antibodies in turn may be labeled and the assay carried out where the duplex is bound to a surface, so that upon the formation

of duplex on the surface, the presence of antibody bound to the duplex can be detected. The use of probes to the novel anti-sense RNA may be carried out in any conventional techniques such as nucleic acid

5 hybridization, plus and minus screening, recombinational probing, hybrid released translation (HRT), and hybrid arrested translation (HART). This also includes amplification techniques such as polymerase chain reaction (PCR).

10 Diagnostic kits which also test for the qualitative or quantitative presence of other markers are also contemplated. Diagnosis or prognosis may depend on the combination of multiple indications used as markers. Thus, kits may test for combinations of markers. See,
15 e.g., Viallet, et al. (1989) Progress in Growth Factor Res. 1:89-97.

VIII. Therapeutic Utility

This invention provides reagents with significant
20 therapeutic value. The DTLRs (naturally occurring or recombinant), fragments thereof, mutein receptors, and antibodies, along with compounds identified as having binding affinity to the receptors or antibodies, should be useful in the treatment of conditions exhibiting abnormal
25 expression of the receptors of their ligands. Such abnormality will typically be manifested by immunological disorders. Additionally, this invention should provide therapeutic value in various diseases or disorders associated with abnormal expression or abnormal triggering
30 of response to the ligand. The Toll ligands have been suggested to be involved in morphologic development, e.g., dorso-ventral polarity determination, and immune responses, particularly the primitive innate responses. See, e.g., Sun, et al. (1991) Eur. J. Biochem. 196:247-
35 254; Hultmark (1994) Nature 367:116-117.

Recombinant DTLRs, muteins, agonist or antagonist antibodies thereto, or antibodies can be purified and then administered to a patient. These reagents can be combined for therapeutic use with additional active ingredients, e.g., in conventional pharmaceutically acceptable carriers or diluents, along with physiologically innocuous stabilizers and excipients. These combinations can be sterile, e.g., filtered, and placed into dosage forms as by lyophilization in dosage vials or storage in stabilized aqueous preparations. This invention also contemplates use of antibodies or binding fragments thereof which are not complement binding.

Ligand screening using DTLR or fragments thereof can be performed to identify molecules having binding affinity to the receptors. Subsequent biological assays can then be utilized to determine if a putative ligand can provide competitive binding, which can block intrinsic stimulating activity. Receptor fragments can be used as a blocker or antagonist in that it blocks the activity of ligand. Likewise, a compound having intrinsic stimulating activity can activate the receptor and is thus an agonist in that it simulates the activity of ligand, e.g., inducing signaling. This invention further contemplates the therapeutic use of antibodies to DTLRs as antagonists.

The quantities of reagents necessary for effective therapy will depend upon many different factors, including means of administration, target site, physiological state of the patient, and other medicaments administered. Thus, treatment dosages should be titrated to optimize safety and efficacy. Typically, dosages used in vitro may provide useful guidance in the amounts useful for in situ administration of these reagents. Animal testing of effective doses for treatment of particular disorders will provide further predictive indication of human dosage. Various considerations are described, e.g., in Gilman, et al. (eds. 1990) Goodman and Gilman's: The Pharmacological

Bases of Therapeutics, 8th Ed., Pergamon Press; and Remington's Pharmaceutical Sciences, (current edition), Mack Publishing Co., Easton, Penn.; each of which is hereby incorporated herein by reference. Methods for administration are discussed therein and below, e.g., for oral, intravenous, intraperitoneal, or intramuscular administration, transdermal diffusion, and others. Pharmaceutically acceptable carriers will include water, saline, buffers, and other compounds described, e.g., in the Merck Index, Merck & Co., Rahway, New Jersey. Because of the likely high affinity binding, or turnover numbers, between a putative ligand and its receptors, low dosages of these reagents would be initially expected to be effective. And the signaling pathway suggests extremely low amounts of ligand may have effect. Thus, dosage ranges would ordinarily be expected to be in amounts lower than 1 mM concentrations, typically less than about 10 μ M concentrations, usually less than about 100 nM, preferably less than about 10 pM (picomolar), and most preferably less than about 1 fM (femtomolar), with an appropriate carrier. Slow release formulations, or slow release apparatus will often be utilized for continuous administration.

DTLRs, fragments thereof, and antibodies or its fragments, antagonists, and agonists, may be administered directly to the host to be treated or, depending on the size of the compounds, it may be desirable to conjugate them to carrier proteins such as ovalbumin or serum albumin prior to their administration. Therapeutic formulations may be administered in any conventional dosage formulation. While it is possible for the active ingredient to be administered alone, it is preferable to present it as a pharmaceutical formulation. Formulations comprise at least one active ingredient, as defined above, together with one or more acceptable carriers thereof. Each carrier must be both pharmaceutically and

physiologically acceptable in the sense of being compatible with the other ingredients and not injurious to the patient. Formulations include those suitable for oral, rectal, nasal, or parenteral (including subcutaneous, intramuscular, intravenous and intradermal) administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. See, e.g., Gilman, et al. (eds. 1990) Goodman and Gilman's: The Pharmacological Bases of Therapeutics, 8th Ed., Pergamon Press; and Remington's Pharmaceutical Sciences (current edition), Mack Publishing Co., Easton, Penn.; Avis, et al. (eds. 1993) Pharmaceutical Dosage Forms: Parenteral Medications Dekker, NY; Lieberman, et al. (eds. 1990) Pharmaceutical Dosage Forms: Tablets Dekker, NY; and Lieberman, et al. (eds. 1990) Pharmaceutical Dosage Forms: Disperse Systems Dekker, NY. The therapy of this invention may be combined with or used in association with other therapeutic agents, particularly agonists or antagonists of other IL-1 family members.

IX. Ligands

The description of the Toll receptors herein provide means to identify ligands, as described above. Such ligand should bind specifically to the respective receptor with reasonably high affinity. Various constructs are made available which allow either labeling of the receptor to detect its ligand. For example, directly labeling DTLR, fusing onto it markers for secondary labeling, e.g., FLAG or other epitope tags, etc., will allow detection of receptor. This can be histological, as an affinity method for biochemical purification, or labeling or selection in an expression cloning approach. A two-hybrid selection system may also be applied making appropriate constructs with the available DTLR sequences. See, e.g., Fields and Song (1989) Nature 340:245-246.

Generally, descriptions of DTLRs will be analogously applicable to individual specific embodiments directed to DTLR2, DTLR3, DTLR4, DTLR5, DTLR6, DTLR7, DTLR8, DTLR9, and/or DTLR10 reagents and compositions.

- 5 The broad scope of this invention is best understood with reference to the following examples, which are not intended to limit the inventions to the specific embodiments.

EXAMPLES

I. General Methods

Some of the standard methods are described or referenced, e.g., in Maniatis, et al. (1982) Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Laboratory, Cold Spring Harbor Press; Sambrook, et al. (1989) Molecular Cloning: A Laboratory Manual, (2d ed.), vols. 1-3, CSH Press, NY; Ausubel, et al., Biology, 10 Greene Publishing Associates, Brooklyn, NY; or Ausubel, et al. (1987 and Supplements) Current Protocols in Molecular Biology, Greene/Wiley, New York. Methods for protein purification include such methods as ammonium sulfate precipitation, column chromatography, electrophoresis, 15 centrifugation, crystallization, and others. See, e.g., Ausubel, et al. (1987 and periodic supplements); Coligan, et al. (ed. 1996) and periodic supplements, Current Protocols In Protein Science Greene/Wiley, New York; Deutscher (1990) "Guide to Protein Purification" in 20 Methods in Enzymology, vol. 182, and other volumes in this series; and manufacturer's literature on use of protein purification products, e.g., Pharmacia, Piscataway, N.J., or Bio-Rad, Richmond, CA. Combination with recombinant techniques allow fusion to appropriate segments, e.g., to 25 a FLAG sequence or an equivalent which can be fused via a protease-removable sequence. See, e.g., Hochuli (1989) Chemische Industrie 12:69-70; Hochuli (1990) "Purification of Recombinant Proteins with Metal Chelate Absorbent" in Setlow (ed.) Genetic Engineering, Principle and Methods 30 12:87-98, Plenum Press, N.Y.; and Crowe, et al. (1992) QIAexpress: The High Level Expression and Protein Purification System QUIAGEN, Inc., Chatsworth, CA.

Standard immunological techniques and assays are described, e.g., in Hertenberg, et al. (eds. 1996) Weir's 35 Handbook of Experimental Immunology vols. 1-4, Blackwell Science; Coligan (1991) Current Protocols in Immunology

Wiley/Greene, NY; and Methods in Enzymology volumes. 70, 73, 74, 84, 92, 93, 108, 116, 121, 132, 150, 162, and 163.

Assays for vascular biological activities are well known in the art. They will cover angiogenic and
5 angiostatic activities in tumor, or other tissues, e.g., arterial smooth muscle proliferation (see, e.g., Koyoma, et al. (1996) Cell 87:1069-1078), monocyte adhesion to vascular epithelium (see McEvoy, et al. (1997) J. Exp. Med. 185:2069-2077), etc. See also Ross (1993) Nature
10 362:801-809; Rekhter and Gordon (1995) Am. J. Pathol. 147:668-677; Thyberg, et al. (1990) Atherosclerosis 10:966-990; and Gumbiner (1996) Cell 84:345-357.

Assays for neural cell biological activities are described, e.g., in Wouterlood (ed. 1995) Neuroscience
15 Protocols modules 10, Elsevier; Methods in Neurosciences Academic Press; and Neuromethods Humana Press, Totowa, NJ. Methodology of developmental systems is described, e.g., in Meisami (ed.) Handbook of Human Growth and
20 Developmental Biology CRC Press; and Chrispeels (ed.) Molecular Techniques and Approaches in Developmental Biology Interscience.

Computer sequence analysis is performed, e.g., using available software programs, including those from the GCG (U. Wisconsin) and GenBank sources. Public sequence
25 databases were also used, e.g., from GenBank, NCBI, EMBO, and others. Determination of transmembrane and other important motifs may be predicted using such bioinformatics tools.

Many techniques applicable to IL-10 receptors may be
30 applied to DTLRs, as described, e.g., in USSN 08/110,683 (IL-10 receptor), which is incorporated herein by reference for all purposes.

II. Novel Family of Human Receptors

35

Abbreviations: DTLR, DNAX Toll-like receptor; IL-1R, interleukin-1 receptor; TH, Toll homology; LRR, leucine-rich repeat; EST, expressed sequence tag; STS, sequence tagged site; FISH, fluorescence in situ hybridization.

5

The discovery of sequence homology between the cytoplasmic domains of *Drosophila* Toll and human interleukin-1 (IL-1) receptors has sown the conviction that both molecules trigger related signaling pathways tied to the nuclear translocation of Rel-type transcription factors. This conserved signaling scheme governs an evolutionarily ancient immune response in both insects and vertebrates. We report the molecular cloning of a novel class of putative human receptors with a protein architecture that is closely similar to *Drosophila* Toll in both intra- and extra-cellular segments. Five human Toll-like receptors, designated DTLRs 1-5, are likely the direct homologs of the fly molecule, and as such could constitute an important and unrecognized component of innate immunity in humans; intriguingly, the evolutionary retention of DTLRs in vertebrates may indicate another role, akin to Toll in the dorso-ventralization of the *Drosophila* embryo, as regulators of early morphogenetic patterning. Multiple tissue mRNA blots indicate markedly different patterns of expression for the human DTLRs. Using fluorescence in situ hybridization and Sequence-Tagged Site database analyses, we also show that the cognate DTLR genes reside on chromosomes 4 (DTLRs 1, 2, and 3), 9 (DTLR4), and 1 (DTLR5). Structure prediction of the aligned Toll-homology (TH) domains from varied insect and human DTLRs, vertebrate IL-1 receptors, and MyD88 factors, and plant disease resistance proteins, recognizes a parallel β/α fold with an acidic active site; a similar structure notably recurs in a class of response regulators broadly involved in transducing sensory information in bacteria.

The seeds of the morphogenetic gulf that so dramatically separates flies from humans are planted in familiar embryonic shapes and patterns, but give rise to very different cell complexities. DeRobertis and Sasai (1996) Nature 380:37-40; and Arendt and Nübler-Jung (1997) Mech. Develop. 61:7-21. This divergence of developmental plans between insects and vertebrates is choreographed by remarkably similar signaling pathways, underscoring a greater conservation of protein networks and biochemical mechanisms from unequal gene repertoires. Miklos and Rubin (1996) Cell 86:521-529; and Chothia (1994) Develop. 1994 Suppl., 27-33. A powerful way to chart the evolutionary design of these regulatory pathways is by inferring their likely molecular components (and biological functions) through interspecies comparisons of protein sequences and structures. Miklos and Rubin (1996) Cell 86:521-529; Chothia (1994) Develop. 1994 Suppl., 27-33 (3-5); and Banfi, et al. (1996) Nature Genet. 13:167-174.

A universally critical step in embryonic development is the specification of body axes, either born from innate asymmetries or triggered by external cues. DeRobertis and Sasai (1996) Nature 380:37-40; and Arendt and Nübler-Jung (1997) Mech. Develop. 61:7-21. As a model system, particular attention has been focused on the phylogenetic basis and cellular mechanisms of dorsoventral polarization. DeRobertis and Sasai (1996) Nature 380:37-40; and Arendt and Nübler-Jung (1997) Mech. Develop. 61:7-21. A prototype molecular strategy for this transformation has emerged from the *Drosophila* embryo, where the sequential action of a small number of genes results in a ventralizing gradient of the transcription factor Dorsal. St. Johnston and Nüsslein-Volhard (1992) Cell 68:201-219; and Morisato and Anderson (1995) Ann. Rev. Genet. 29:371-399.

This signaling pathway centers on Toll, a transmembrane receptor that transduces the binding of a maternally-secreted ventral factor, Spätzle, into the cytoplasmic engagement of Tube, an accessory molecule, and the activation of Pelle, a Ser/Thr-kinase that catalyzes the dissociation of Dorsal from the inhibitor Cactus and allows migration of Dorsal to ventral nuclei (Morisato and Anderson (1995) Ann. Rev. Genet. 29:371-399; and Belvin and Anderson (1996) Ann. Rev. Cell Develop. Biol. 12:393-416. The Toll pathway also controls the induction of potent antimicrobial factors in the adult fly (Lemaitre, et al. (1996) Cell 86:973-983); this role in *Drosophila* immune defense strengthens mechanistic parallels to IL-1 pathways that govern a host of immune and inflammatory responses in vertebrates. Belvin and Anderson (1996) Ann. Rev. Cell Develop. Biol. 12:393-416; and Wasserman (1993) Molec. Biol. Cell 4:767-771. A Toll-related cytoplasmic domain in IL-1 receptors directs the binding of a Pelle-like kinase, IRAK, and the activation of a latent NF- κ B/I- κ B complex that mirrors the embrace of Dorsal and Cactus. Belvin and Anderson (1996) Ann. Rev. Cell Develop. Biol. 12:393-416; and Wasserman (1993) Molec. Biol. Cell 4:767-771.

We describe the cloning and molecular characterization of four new Toll-like molecules in humans, designated DTLRs 2-5 (following Chiang and Beachy (1994) Mech. Develop. 47:225-239), that reveal a receptor family more closely tied to *Drosophila* Toll homologs than to vertebrate IL-1 receptors. The DTLR sequences are derived from human ESTs; these partial cDNAs were used to draw complete expression profiles in human tissues for the five DTLRs, map the chromosomal locations of cognate genes, and narrow the choice of cDNA libraries for full-length cDNA retrievals. Spurred by other efforts (Banfi, et al. (1996) Nature Genet. 13:167-174; and Wang, et al. (1996) J. Biol. Chem. 271:4468-4476), we are assembling,

by structural conservation and molecular parsimony, a biological system in humans that is the counterpart of a compelling regulatory scheme in *Drosophila*. In addition, a biochemical mechanism driving Toll signaling is suggested by the proposed tertiary fold of the Toll-homology (TH) domain, a core module shared by DTLRs, a broad family of IL-1 receptors, mammalian MyD88 factors and plant disease resistance proteins. Mitcham, et al. (1996) J. Biol. Chem. 271:5777-5783; and Hardiman, et al. (1996) Oncogene 13:2467-2475. We propose that a signaling route coupling morphogenesis and primitive immunity in insects, plants, and animals (Belvin and Anderson (1996) Ann. Rev. Cell Develop. Biol. 12:393-416; and Wilson, et al. (1997) Curr. Biol. 7:175-178) may have roots in bacterial two-component pathways.

Computational Analysis.

Human sequences related to insect DTLRs were identified from the EST database (dbEST) at the National Center for Biotechnology Information (NCBI) using the BLAST server (Altschul, et al. (1994) Nature Genet. 6:119-129). More sensitive pattern- and profile-based methods (Bork and Gibson (1996) Meth. Enzymol. 266:162-184) were used to isolate the signaling domains of the DTLR family that are shared with vertebrate and plant proteins present in nonredundant databases. The progressive alignment of DTLR intra- or extracellular domain sequences was carried out by ClustalW (Thompson, et al. (1994) Nucleic Acids Res. 22:4673-4680); this program also calculated the branching order of aligned sequences by the Neighbor-Joining algorithm (5000 bootstrap replications provided confidence values for the tree groupings).

Conserved alignment patterns, discerned at several degrees of stringency, were drawn by the Consensus program (internet URL <http://www.bork.embl-heidelberg.de/Alignment/consensus.html>). The PRINTS

library of protein fingerprints
(<http://www.biochem.ucl.ac.uk/bsm/dbbrowser/PRINTS/PRINTS.html>) (Attwood, et al. (1997) Nucleic Acids Res. 25:212-217) reliably identified the myriad leucine-rich
5 repeats (LRRs) present in the extracellular segments of DTLRs with a compound motif (PRINTS code Leurichrpt) that flexibly matches N- and C-terminal features of divergent LRRs. Two prediction algorithms whose three-state accuracy is above 72% were used to derive a consensus
10 secondary structure for the intracellular domain alignment, as a bridge to fold recognition efforts (Fischer, et al. (1996) FASEB J. 10:126-136). Both the neural network program PHD (Rost and Sander (1994) Proteins 19:55-72) and the statistical prediction method
15 DSC (King and Sternberg (1996) Protein Sci. 5:2298-2310) have internet servers (URLs http://www.embl-heidelberg.de/predictprotein/phd_pred.html and http://bonsai.lif.icnet.uk/bmm/dsc/dsc_read_align.html, respectively). The intracellular region encodes the THD
20 region discussed, e.g., in Hardimar, et al. (1996) Oncogene 13:2467-2475; and Rock, et al. (1998) Proc. Nat'l Acad. Sci. USA 95:588-593, each of which is incorporated herein by reference. This domain is very important in the mechanism of signaling by the receptors, which transfers a
25 phosphate group to a substrate.

Cloning of full-length human DTLR cDNAs.

PCR primers derived from the Toll-like Humrsc786 sequence (GenBank accession code D13637) (Nomura, et al.
30 (1994) DNA Res. 1:27-35) were used to probe a human erythroleukemic, TF-1 cell line-derived cDNA library (Kitamura, et al. (1989) Blood 73:375-380) to yield the DTLR1 cDNA sequence. The remaining DTLR sequences were flagged from dbEST, and the relevant EST clones obtained
35 from the I.M.A.G.E. consortium (Lennon, et al. (1996) Genomics 33:151-152) via Research Genetics (Huntsville,

AL): CloneID#'s 80633 and 117262 (DTLR2), 144675 (DTLR3), 202057 (DTLR4) and 277229 (DTLR5). Full length cDNAs for human DTLRs 2-4 were cloned by DNA hybridization screening of λ gt10 phage, human adult lung, placenta, and fetal liver 5'-Stretch Plus cDNA libraries (Clontech), respectively; the DTLR5 sequence is derived from a human multiple-sclerosis plaque EST. All positive clones were sequenced and aligned to identify individual DTLR ORFs: DTLR1 (2366 bp clone, 786 aa ORF), DTLR2 (2600 bp, 784 aa), DTLR3 (3029 bp, 904 aa), DTLR4 (3811 bp, 879 aa) and DTLR5 (1275 bp, 370 aa). Similar methods are used for DTLRs 6-10. Probes for DTLR3 and DTLR4 hybridizations were generated by PCR using human placenta (Stratagene) and adult liver (Clontech) cDNA libraries as templates, respectively; primer pairs were derived from the respective EST sequences. PCR reactions were conducted using *T. aquaticus* Taqplus DNA polymerase (Stratagene) under the following conditions: 1 x (94° C, 2 min) 30 x (55° C, 20 sec; 72° C 30 sec; 94° C 20 sec), 1 x (72° C, 8 min). For DTLR2 full-length cDNA screening, a 900 bp fragment generated by EcoRI/XbaI digestion of the first EST clone (ID# 80633) was used as a probe.

mRNA blots and chromosomal localization.

Human multiple tissue (Cat# 1, 2) and cancer cell line blots (Cat# 7757-1), containing approximately 2 μ g of poly(A)⁺ RNA per lane, were purchased from Clontech (Palo Alto, CA). For DTLRs 1-4, the isolated full-length cDNAs served as probes, for DTLR5 the EST clone (ID #277229) plasmid insert was used. Briefly, the probes were radiolabeled with [α -³²P] dATP using the Amersham Rediprime random primer labeling kit (RPN1633). Prehybridization and hybridizations were performed at 65° C in 0.5 M Na₂HPO₄, 7% SDS, 0.5 M EDTA (pH 8.0). All stringency washes were conducted at 65° C with two initial washes in 2 x SSC, 0.1% SDS for 40 min followed by a

subsequent wash in 0.1 x SSC, 0.1% SDS for 20 min. Membranes were then exposed at -70° C to X-Ray film (Kodak) in the presence of intensifying screens. More detailed studies by cDNA library Southern (14) were performed with selected human DTLR clones to examine their expression in hemopoietic cell subsets.

Human chromosomal mapping was conducted by the method of fluorescence in situ hybridization (FISH) as described in Heng and Tsui (1994) Meth. Molec. Biol. 33:109-122, using the various full-length (DTLRs 2-4) or partial (DTLR5) cDNA clones as probes. These analyses were performed as a service by SeeDNA Biotech Inc. (Ontario, Canada). A search for human syndromes (or mouse defects in syntenic loci) associated with the mapped DTLR genes was conducted in the Dysmorphic Human-Mouse Homology Database by internet server (http://www.hgmp.mrc.ac.uk/DHMH/ hum_chromel.html). Similar methods are applicable to DTLRs 6-10.

Conserved architecture of insect and human DTLR ectodomains.

The Toll family in *Drosophila* comprises at least four distinct gene products: Toll, the prototype receptor involved in dorsoventral patterning of the fly embryo (Morisato and Anderson (1995) Ann. Rev. Genet. 29:371-399) and a second named '18 Wheeler' (18w) that may also be involved in early embryonic development (Chiang and Beachy (1994) Mech. Develop. 47:225-239; Eldon, et al. (1994) Develop. 120:885-899); two additional receptors are predicted by incomplete, Toll-like ORFs downstream of the male-specific-transcript (Mst) locus (GenBank code X67703) or encoded by the 'sequence-tagged-site' (STS) Dm2245 (GenBank code G01378) (Mitcham, et al. (1996) J. Biol. Chem. 271:5777-5783). The extracellular segments of Toll and 18w are distinctively composed of imperfect, ~24 amino acid LRR motifs (Chiang and Beachy (1994) Mech. Develop.

47:225-239; and Eldon, et al. (1994) Develop. 120:885-899). Similar tandem arrays of LRRs commonly form the adhesive antennae of varied cell surface molecules and their generic tertiary structure is presumed to mimic the
5 horseshoe-shaped cradle of a ribonuclease inhibitor fold, where seventeen LRRs show a repeating β/α -hairpin, 28 residue motif (Buchanan and Gay (1996) Prog. Biophys. Molec. Biol. 65:1-44). The specific recognition of Spätzle by Toll may follow a model proposed for the
10 binding of cystine-knot fold glycoprotein hormones by the multi-LRR ectodomains of serpentine receptors, using the concave side of the curved β -sheet (Kajava, et al. (1995) Structure 3:867-877); intriguingly, the pattern of cysteines in Spätzle, and an orphan *Drosophila* ligand,
15 Trunk, predict a similar cystine-knot tertiary structure (Belvin and Anderson (1996) Ann. Rev. Cell Develop. Biol. 12:393-416; and Casanova, et al. (1995) Genes Develop. 9:2539-2544).

The 22 and 31 LRR ectodomains of Toll and 18w,
20 respectively (the Mst ORF fragment displays 16 LRRs), are most closely related to the comparable 18, 19, 24, and 22 LRR arrays of DTLRs 1-4 (the incomplete DTLR5 chain presently includes four membrane-proximal LRRs) by sequence and pattern analysis (Altschul, et al. (1994)
25 Nature Genet. 6:119-129; and Bork and Gibson (1996) Meth. Enzymol. 266:162-184) (Fig. 1). However, a striking difference in the human DTLR chains is the common loss of a ~90 residue cysteine-rich region that is variably embedded in the ectodomains of Toll, 18w and the Mst ORF
30 (distanced four, six and two LRRs, respectively, from the membrane boundary). These cysteine clusters are bipartite, with distinct 'top' (ending an LRR) and 'bottom' (stacked atop an LRR) halves (Chiang and Beachy (1994) Mech. Develop. 47:225-239; Eldon, et al. (1994)
35 Develop. 120:885-899; and Buchanan and Gay (1996) Prog. Biophys. Molec. Biol. 65:1-44); the 'top' module recurs in

both Drosophila and human DTLRs as a conserved juxtamembrane spacer (Fig. 1). We suggest that the flexibly located cysteine clusters in Drosophila receptors (and other LRR proteins), when mated 'top' to 'bottom',
5 form a compact module with paired termini that can be inserted between any pair of LRRs without altering the overall fold of DTLR ectodomains; analogous 'extruded' domains decorate the structures of other proteins (Russell (1994) Protein Engin. 7:1407-1410).

10

Molecular design of the TH signaling domain.

Sequence comparison of Toll and IL-1 type-I (IL-1R1) receptors has disclosed a distant resemblance of a ~200 amino acid cytoplasmic domain that presumably mediates
15 signaling by similar Rel-type transcription factors. Belvin and Anderson (1996) Ann. Rev. Cell Develop. Biol. 12:393-416; and (Belvin and Anderson (1996) Ann. Rev. Cell Develop. Biol. 12:393-416; and Wasserman (1993) Molec. Biol. Cell 4:767-771). More recent additions to
20 this functional paradigm include a pair of plant disease resistance proteins from tobacco and flax that feature an N-terminal TH module followed by nucleotide-binding (NTPase) and LRR segments (Wilson, et al. (1997) Curr. Biol. 7:175-178); by contrast, a 'death domain' precedes
25 the TH chain of MyD88, an intracellular myeloid differentiation marker (Mitcham, et al. (1996) J. Biol. Chem. 271:5777-5783; and Hardiman, et al. (1996) Oncogene 13:2467-2475) (Fig. 1). New IL-1-type receptors include
30 IL-1R3, an accessory signaling molecule, and orphan receptors IL-1R4 (also called ST2/Fit-1/T1), IL-1R5 (IL-1R-related protein), and IL-1R6 (IL-1R-related protein-2) (Mitcham, et al. (1996) J. Biol. Chem. 271:5777-5783; Hardiman, et al. (1996) Oncogene 13:2467-2475). With
35 the new human DTLR sequences, we have sought a structural definition of this evolutionary thread by analyzing the conformation of the common TH module: ten blocks of

conserved sequence comprising 128 amino acids form the minimal TH domain fold; gaps in the alignment mark the likely location of sequence and length-variable loops (Fig. 2A-2B).

5 Two prediction algorithms that take advantage of the patterns of conservation and variation in multiply aligned sequences, PHD (Rost and Sander (1994) Proteins 19:55-72) and DSC (King and Sternberg (1996) Protein Sci. 5:2298-2310), produced strong, concordant results for the TH
10 signaling module (Fig. 2A-2B). Each block contains a discrete secondary structural element: the imprint of alternating β -strands (labeled A-E) and α -helices (numbered 1-5) is diagnostic of a β/α -class fold with α -helices on both faces of a parallel β -sheet. Hydrophobic
15 β -strands A, C and D are predicted to form 'interior' staves in the β -sheet, while the shorter, amphipathic β -strands B and E resemble typical 'edge' units (Fig. 2A-2B). This assignment is consistent with a strand order of B-A-C-D-E in the core β -sheet (Fig. 2C); fold comparison
20 ('mapping') and recognition ('threading') programs (Fischer, et al. (1996) FASEB J. 10:126-136) strongly return this doubly wound β/α topology. A surprising, functional prediction of this outline structure for the TH domain is that many of the conserved, charged residues in
25 the multiple alignment map to the C-terminal end of the β -sheet: residue Asp16 (block numbering scheme - Fig. 2A-2B) at the end of β A, Arg39 and Asp40 following β B, Glu75 in the first turn of α 3, and the more loosely conserved Glu/Asp residues in the β D- α 4 loop, or after β E (Fig. 2A-2B). The location of four other conserved residues (Asp7,
30 Glu28, and the Arg57-Arg/Lys58 pair) is compatible with a salt bridge network at the opposite, N-terminal end of the β -sheet (Fig. 2A-2B). Alignment of the other DTLR embodiments exhibit similar features, and peptide segments
35 comprising these features, e.g., 20 amino acid segments containing them, are particularly important.

Signaling function depends on the structural integrity of the TH domain. Inactivating mutations or deletions within the module boundaries (Fig. 2A-2B) have been catalogued for IL-1R1 and Toll. Heguy, et al. (1992) J. Biol. Chem. 267:2605-2609; Croston, et al. (1995) J. Biol. Chem. 270:16514-16517; Schneider, et al. (1991) Genes Develop. 5:797-807; Norris and Manley. (1992) Genes Develop. 6:1654-1667; Norris and Manley (1995) Genes Develop. 9:358-369; and Norris and Manley (1996) Genes Develop. 10:862-872. The human DTLR1-5 chains extending past the minimal TH domain (8, 0, 6, 22 and 18 residue lengths, respectively) are most closely similar to the stubby, 4 aa 'tail' of the Mst ORF. Toll and 18w display unrelated 102 and 207 residue tails (Fig. 2A-2B) that may negatively regulate the signaling of the fused TH domains. Norris and Manley (1995) Genes Develop. 9:358-369; and Norris and Manley (1996) Genes Develop. 10:862-872.

The evolutionary relationship between the disparate proteins that carry the TH domain can best be discerned by a phylogenetic tree derived from the multiple alignment (Fig. 3). Four principal branches segregate the plant proteins, the MyD88 factors, IL-1 receptors, and Toll-like molecules; the latter branch clusters the Drosophila and human DTLRs.

Chromosomal dispersal of human DTLR genes.

In order to investigate the genetic linkage of the nascent human DTLR gene family, we mapped the chromosomal loci of four of the five genes by FISH (Fig. 4). The DTLR1 gene has previously been charted by the human genome project: an STS database locus (dbSTS accession number G06709, corresponding to STS WI-7804 or SHGC-12827) exists for the Humrsc786 cDNA (Nomura, et al. (1994) DNA Res. 1:27-35) and fixes the gene to chromosome 4 marker interval D4S1587-D42405 (50-56 cM) circa 4p14. This assignment has recently been corroborated by FISH

analysis. Taguchi, et al. (1996) Genomics 32:486-488. In the present work, we reliably assign the remaining DTLR genes to loci on chromosome 4q32 (DTLR2), 4q35 (DTLR3), 9q32-33 (DTLR4) and 1q33.3 (DTLR5). During the course of this work, an STS for the parent DTLR2 EST (cloneID # 80633) has been generated (dbSTS accession number T57791 for STS SHGC-33147) and maps to the chromosome 4 marker interval D4S424-D4S1548 (143-153 cM) at 4q32 -in accord with our findings. There is a ~50 cM gap between DTLR2 and DTLR3 genes on the long arm of chromosome 4.

DTLR genes are differentially expressed.

Both Toll and 18w have complex spatial and temporal patterns of expression in *Drosophila* that may point to functions beyond embryonic patterning. St. Johnston and Nüsslein-Volhard (1992) Cell 68:201-219; Morisato and Anderson (1995) Ann. Rev. Genet. 29:371-399; Belvin and Anderson (1996) Ann. Rev. Cell Develop. Biol. 12:393-416; Lemaitre, et al. (1996) Cell 86:973-983; Chiang and Beachy (1994) Mech. Develop. 47:225-239; and Eldon, et al. (1994) Develop. 120:885-899. We have examined the spatial distribution of DTLR transcripts by mRNA blot analysis with varied human tissue and cancer cell lines using radiolabeled DTLR cDNAs (Fig. 5). DTLR1 is found to be ubiquitously expressed, and at higher levels than the other receptors. Presumably reflecting alternative splicing, 'short' 3.0 kB and 'long' 8.0 kB DTLR1 transcript forms are present in ovary and spleen, respectively (Fig. 5, panels A and B). A cancer cell mRNA panel also shows the prominent overexpression of DTLR1 in a Burkitt's Lymphoma Raji cell line (Fig. 5, panel C). DTLR2 mRNA is less widely expressed than DTLR1, with a 4.0 kB species detected in lung and a 4.4 kB transcript evident in heart, brain and muscle. The tissue distribution pattern of DTLR3 echoes that of DTLR2 (Fig. 5, panel E). DTLR3 is also present as two major

transcripts of approximately 4.0 and 6.0 kB in size, and the highest levels of expression are observed in placenta and pancreas. By contrast, DTLR4 and DTLR5 messages appear to be extremely tissue-specific. DTLR4 was
5 detected only in placenta as a single transcript of ~7.0 kB in size. A faint 4.0 kB signal was observed for DTLR5 in ovary and peripheral blood monocytes.

Components of an evolutionarily ancient regulatory system.
10 The original molecular blueprints and divergent fates of signaling pathways can be reconstructed by comparative genomic approaches. Miklos and Rubin (1996) Cell 86:521-529; Chothia (1994) Develop. 1994 Suppl., 27-33; Banfi, et al. (1996) Nature Genet. 13:167-174; and Wang, et al.
15 (1996) J. Biol. Chem. 271:4468-4476. We have used this logic to identify an emergent gene family in humans, encoding five receptor paralogs at present, DTLRs 1-5, that are the direct evolutionary counterparts of a *Drosophila* gene family headed by Toll (Figs. 1-3). The
20 conserved architecture of human and fly DTLRs, conserved LRR ectodomains and intracellular TH modules (Fig. 1), intimates that the robust pathway coupled to Toll in *Drosophila* (6, 7) survives in vertebrates. The best evidence borrows from a reiterated pathway: the manifold
25 IL-1 system and its repertoire of receptor-fused TH domains, IRAK, NF- κ B and I- κ B homologs (Belvin and Anderson (1996) Ann. Rev. Cell Develop. Biol. 12:393-416; Wasserman (1993) Molec. Biol. Cell 4:767-771; Hardiman, et al. (1996) Oncogene 13:2467-2475; and Cao, et al. (1996)
30 Science 271:1128-1131); a Tube-like factor has also been characterized. It is not known whether DTLRs can productively couple to the IL-1R signaling machinery, or instead, a parallel set of proteins is used. Differently from IL-1 receptors, the LRR cradle of human DTLRs is
35 predicted to retain an affinity for Spätzle/Trunk-related

cystine-knot factors; candidate DTLR ligands (called PENs) that fit this mold have been isolated.

Biochemical mechanisms of signal transduction can be gauged by the conservation of interacting protein folds in a pathway. Miklos and Rubin (1996) Cell 86:521-529; Chothia (1994) Develop. 1994 Suppl., 27-33. At present, the Toll signaling paradigm involves some molecules whose roles are narrowly defined by their structures, actions or fates: Pelle is a Ser/Thr kinase (phosphorylation), Dorsal is an NF- κ B-like transcription factor (DNA-binding) and Cactus is an ankyrin-repeat inhibitor (Dorsal binding, degradation). Belvin and Anderson (1996) Ann. Rev. Cell Develop. Biol. 12:393-416. By contrast, the functions of the Toll TH domain and Tube remain enigmatic. Like other cytokine receptors (Heldin (1995) Cell 80:213-223), ligand-mediated dimerization of Toll appears to be the triggering event: free cysteines in the juxtamembrane region of Toll create constitutively active receptor pairs (Schneider, et al. (1991) Genes Develop. 5:797-807), and chimeric Torso-Toll receptors signal as dimers (Galindo, et al. (1995) Develop. 121:2209-2218); yet, severe truncations or wholesale loss of the Toll ectodomain results in promiscuous intracellular signaling (Norris and Manley (1995) Genes Develop. 9:358-369; and Winans and Hashimoto (1995) Molec. Biol. Cell 6:587-596), reminiscent of oncogenic receptors with catalytic domains (Heldin (1995) Cell 80:213-223). Tube is membrane-localized, engages the N-terminal (death) domain of Pelle and is phosphorylated, but neither Toll-Tube or Toll-Pelle interactions are registered by two-hybrid analysis (Galindo, et al. (1995) Develop. 121:2209-2218; and Großhans, et al. (1994) Nature 372:563-566); this latter result suggests that the conformational 'state' of the Toll TH domain somehow affects factor recruitment. Norris and Manley (1996) Genes Develop. 10:862-872; and Galindo, et al. (1995) Develop. 121:2209-2218.

At the heart of these vexing issues is the structural nature of the Toll TH module. To address this question, we have taken advantage of the evolutionary diversity of TH sequences from insects, plants and vertebrates, incorporating the human DTLR chains, and extracted the minimal, conserved protein core for structure prediction and fold recognition (Fig. 2). The strongly predicted (β/α)₅ TH domain fold with its asymmetric cluster of acidic residues is topologically identical to the structures of response regulators in bacterial two-component signaling pathways (Volz (1993) Biochemistry 32:11741-11753; and Parkinson (1993) Cell 73:857-871) (Fig. 2A-2C). The prototype chemotaxis regulator CheY transiently binds a divalent cation in an 'aspartate pocket' at the C-end of the core β -sheet; this cation provides electrostatic stability and facilitates the activating phosphorylation of an invariant Asp. Volz (1993) Biochemistry 32:11741-11753. Likewise, the TH domain may capture cations in its acidic nest, but activation, and downstream signaling, could depend on the specific binding of a negatively charged moiety: anionic ligands can overcome intensely negative binding-site potentials by locking into precise hydrogen-bond networks. Ledvina, et al. (1996) Proc. Natl. Acad. Sci. USA 93:6786-6791. Intriguingly, the TH domain may not simply act as a passive scaffold for the assembly of a Tube/Pelle complex for Toll, or homologous systems in plants and vertebrates, but instead actively participate as a true conformational trigger in the signal transducing machinery. Perhaps explaining the conditional binding of a Tube/Pelle complex, Toll dimerization could promote unmasking, by regulatory receptor tails (Norris and Manley (1995) Genes Develop. 9:358-369; Norris and Manley (1996) Genes Develop. 10:862-872), or binding by small molecule activators of the TH pocket. However, 'free' TH modules inside the cell (Norris and Manley (1995) Genes Develop. 9:358-369; Winans and Hashimoto

(1995) Molec. Biol. Cell 6:587-596) could act as catalytic, CheY-like triggers by activating and docking with errant Tube/Pelle complexes.

5 Morphogenetic receptors and immune defense.

The evolutionary link between insect and vertebrate immune systems is stamped in DNA: genes encoding antimicrobial factors in insects display upstream motifs similar to acute phase response elements known to bind NF-
10 kB transcription factors in mammals. Hultmark (1993) Trends Genet. 9:178-183. Dorsal, and two Dorsal-related factors, Dif and Relish, help induce these defense proteins after bacterial challenge (Reichhart, et al. (1993) C. R. Acad. Sci. Paris 316:1218-1224; Ip, et al. (1993) Cell 75:753-763; and Dushay, et al. (1996) Proc. Natl. Acad. Sci. USA 93:10343-10347); Toll, or other DTLRs, likely modulate these rapid immune responses in adult *Drosophila* (Lemaitre, et al. (1996) Cell 86:973-983; and Rosetto, et al. (1995) Biochem. Biophys. Res. Commun. 209:111-116). These mechanistic parallels to the IL-1 inflammatory response in vertebrates are evidence of the functional versatility of the Toll signaling pathway, and suggest an ancient synergy between embryonic patterning and innate immunity (Belvin and Anderson (1996) Ann. Rev. Cell Develop. Biol. 12:393-416; Lemaitre, et al. (1996) Cell 86:973-983; Wasserman (1993) Molec. Biol. Cell 4:767-771; Wilson, et al. (1997) Curr. Biol. 7:175-178; Hultmark (1993) Trends Genet. 9:178-183; Reichhart, et al. (1993) C. R. Acad. Sci. Paris 316:1218-1224; Ip, et al. (1993) Cell 75:753-763; Dushay, et al. (1996) Proc. Natl. Acad. Sci. USA 93:10343-10347; Rosetto, et al. (1995) Biochem. Biophys. Res. Commun. 209:111-116; Medzhitov and Janeway (1997) Curr. Opin. Immunol. 9:4-9; and Medzhitov and Janeway (1997) Curr. Opin. Immunol. 9:4-9). The closer
35 homology of insect and human DTLR proteins invites an even stronger overlap of biological functions that supersedes

the purely immune parallels to IL-1 systems, and lends potential molecular regulators to dorso-ventral and other transformations of vertebrate embryos. DeRobertis and Sasai (1996) Nature 380:37-40; and Arendt and Nübler-Jung
5 (1997) Mech. Develop. 61:7-21.

The present description of an emergent, robust receptor family in humans mirrors the recent discovery of the vertebrate Frizzled receptors for Wnt patterning factors. Wang, et al. (1996) J. Biol. Chem. 271:4468-
10 4476. As numerous other cytokine-receptor systems have roles in early development (Lemaire and Kodjabachian (1996) Trends Genet. 12:525-531), perhaps the distinct cellular contexts of compact embryos and gangly adults simply result in familiar signaling pathways and their
15 diffusible triggers having different biological outcomes at different times, e.g., morphogenesis versus immune defense for DTLRs. For insect, plant, and human Toll-related systems (Hardiman, et al. (1996) Oncogene 13:2467-2475; Wilson, et al. (1997) Curr. Biol. 7:175-178), these
20 signals course through a regulatory TH domain that intriguingly resembles a bacterial transducing engine (Parkinson (1993) Cell 73:857-871).

In particular, the DTLR6 exhibits structural features which establish its membership in the family. Moreover,
25 members of the family have been implicated in a number of significant developmental disease conditions and with function of the innate immune system. In particular, the DTLR6 has been mapped to the X chromosome to a location which is a hot spot for major developmental abnormalities.
30 See, e.g., The Sanger Center: human X chromosome website <http://www.sanger.ac.uk/HGP/ChrX/index.shtml>; and the Baylor College of Medicine Human Genome Sequencing website <http://gc.bcm.tmc.edu:8088/cgi-bin/seq/home>.

The accession number for the deposited PAC is
35 AC003046. This accession number contains sequence from two PACs: RPC-164K3 and RPC-263P4. These two PAC

sequences mapped on human chromosome Xp22 at the Baylor web site between STS markers DXS704 and DXS7166. This region is a "hot spot" for severe developmental abnormalities.

5

III. Amplification of DTLR fragment by PCR

Two appropriate primer sequences are selected (see Tables 1 through 10). RT-PCR is used on an appropriate mRNA sample selected for the presence of message to
10 produce a partial or full length cDNA, e.g., a sample which expresses the gene. See, e.g., Innis, et al. (eds. 1990) PCR Protocols: A Guide to Methods and Applications Academic Press, San Diego, CA; and Dieffenbach and Dveksler (eds. 1995) PCR Primer: A Laboratory Manual Cold
15 Spring Harbor Press, CSH, NY. Such will allow determination of a useful sequence to probe for a full length gene in a cDNA library. The DTLR6 is a contiguous sequence in the genome, which may suggest that the other DTLRs are also. Thus, PCR on genomic DNA may yield full
20 length contiguous sequence, and chromosome walking methodology would then be applicable. Alternatively, sequence databases will contain sequence corresponding to portions of the described embodiments, or closely related forms, e.g., alternative splicing, etc. Expression
25 cloning techniques also may be applied on cDNA libraries.

IV. Tissue distribution of DTLRs

Message for each gene encoding these DTLRs has been detected. See Figures 5A-5F. Other cells and tissues
30 will be assayed by appropriate technology, e.g., PCR, immunoassay, hybridization, or otherwise. Tissue and organ cDNA preparations are available, e.g., from Clontech, Mountain View, CA. Identification of sources of natural expression are useful, as described.

35 Southern Analysis: DNA (5 µg) from a primary amplified cDNA library is digested with appropriate restriction

enzymes to release the inserts, run on a 1% agarose gel and transferred to a nylon membrane (Schleicher and Schuell, Keene, NH).

Samples for human mRNA isolation would typically include, e.g.: peripheral blood mononuclear cells (monocytes, T cells, NK cells, granulocytes, B cells), resting (T100); peripheral blood mononuclear cells, activated with anti-CD3 for 2, 6, 12 h pooled (T101); T cell, TH0 clone Mot 72, resting (T102); T cell, TH0 clone Mot 72, activated with anti-CD28 and anti-CD3 for 3, 6, 12 h pooled (T103); T cell, TH0 clone Mot 72, anergic treated with specific peptide for 2, 7, 12 h pooled (T104); T cell, TH1 clone HY06, resting (T107); T cell, TH1 clone HY06, activated with anti-CD28 and anti-CD3 for 3, 6, 12 h pooled (T108); T cell, TH1 clone HY06, anergic treated with specific peptide for 2, 6, 12 h pooled (T109); T cell, TH2 clone HY935, resting (T110); T cell, TH2 clone HY935, activated with anti-CD28 and anti-CD3 for 2, 7, 12 h pooled (T111); T cells CD4+CD45RO- T cells polarized 27 days in anti-CD28, IL-4, and anti IFN- γ , TH2 polarized, activated with anti-CD3 and anti-CD28 4 h (T116); T cell tumor lines Jurkat and Hut78, resting (T117); T cell clones, pooled AD130.2, Tc783.12, Tc783.13, Tc783.58, Tc782.69, resting (T118); T cell random $\gamma\delta$ T cell clones, resting (T119); Splenocytes, resting (B100); Splenocytes, activated with anti-CD40 and IL-4 (B101); B cell EBV lines pooled WT49, RSB, JY, CVIR, 721.221, RM3, HSY, resting (B102); B cell line JY, activated with PMA and ionomycin for 1, 6 h pooled (B103); NK 20 clones pooled, resting (K100); NK 20 clones pooled, activated with PMA and ionomycin for 6 h (K101); NKL clone, derived from peripheral blood of LGL leukemia patient, IL-2 treated (K106); NK cytotoxic clone 640-A30-1, resting (K107); hematopoietic precursor line TF1, activated with PMA and ionomycin for 1, 6 h pooled (C100); U937 premonocytic line, resting (M100); U937 premonocytic line, activated

- with PMA and ionomycin for 1, 6 h pooled (M101);
elutriated monocytes, activated with LPS, IFN γ , anti-IL-10
for 1, 2, 6, 12, 24 h pooled (M102); elutriated monocytes,
activated with LPS, IFN γ , IL-10 for 1, 2, 6, 12, 24 h
5 pooled (M103); elutriated monocytes, activated with LPS,
IFN γ , anti-IL-10 for 4, 16 h pooled (M106); elutriated
monocytes, activated with LPS, IFN γ , IL-10 for 4, 16 h
pooled (M107); elutriated monocytes, activated LPS for 1 h
(M108); elutriated monocytes, activated LPS for 6 h
10 (M109); DC 70% CD1a+, from CD34+ GM-CSF, TNF α 12 days,
resting (D101); DC 70% CD1a+, from CD34+ GM-CSF, TNF α 12
days, activated with PMA and ionomycin for 1 hr (D102); DC
70% CD1a+, from CD34+ GM-CSF, TNF α 12 days, activated with
PMA and ionomycin for 6 hr (D103); DC 95% CD1a+, from
15 CD34+ GM-CSF, TNF α 12 days FACS sorted, activated with PMA
and ionomycin for 1, 6 h pooled (D104); DC 95% CD14+, ex
CD34+ GM-CSF, TNF α 12 days FACS sorted, activated with PMA
and ionomycin 1, 6 hr pooled (D105); DC CD1a+ CD86+, from
CD34+ GM-CSF, TNF α 12 days FACS sorted, activated with PMA
20 and ionomycin for 1, 6 h pooled (D106); DC from monocytes
GM-CSF, IL-4 5 days, resting (D107); DC from monocytes GM-
CSF, IL-4 5 days, resting (D108); DC from monocytes GM-
CSF, IL-4 5 days, activated LPS 4, 16 h pooled (D109); DC
from monocytes GM-CSF, IL-4 5 days, activated TNF α ,
25 monocyte supe for 4, 16 h pooled (D110); leiomyoma L11
benign tumor (X101); normal myometrium M5 (O115);
malignant leiomyosarcoma GS1 (X103); lung fibroblast
sarcoma line MRC5, activated with PMA and ionomycin for 1,
6 h pooled (C101); kidney epithelial carcinoma cell line
30 CHA, activated with PMA and ionomycin for 1, 6 h pooled
(C102); kidney fetal 28 wk male (O100); lung fetal 28 wk
male (O101); liver fetal 28 wk male (O102); heart fetal 28
wk male (O103); brain fetal 28 wk male (O104); gallbladder
fetal 28 wk male (O106); small intestine fetal 28 wk male
35 (O107); adipose tissue fetal 28 wk male (O108); ovary
fetal 25 wk female (O109); uterus fetal 25 wk female

(O110); testes fetal 28 wk male (O111); spleen fetal 28 wk male (O112); adult placenta 28 wk (O113); and tonsil inflamed, from 12 year old (X100).

- Samples for mouse mRNA isolation can include, e.g.:
- 5 resting mouse fibroblastic L cell line (C200); Braf:ER (Braf fusion to estrogen receptor) transfected cells, control (C201); T cells, TH1 polarized (Mel14 bright, CD4+ cells from spleen, polarized for 7 days with IFN- γ and anti IL-4; T200); T cells, TH2 polarized (Mel14 bright,
 - 10 CD4+ cells from spleen, polarized for 7 days with IL-4 and anti-IFN- γ ; T201); T cells, highly TH1 polarized (see Openshaw, et al. (1995) J. Exp. Med. 182:1357-1367; activated with anti-CD3 for 2, 6, 16 h pooled; T202); T cells, highly TH2 polarized (see Openshaw, et al. (1995)
 - 15 J. Exp. Med. 182:1357-1367; activated with anti-CD3 for 2, 6, 16 h pooled; T203); CD44- CD25+ pre T cells, sorted from thymus (T204); TH1 T cell clone D1.1, resting for 3 weeks after last stimulation with antigen (T205); TH1 T cell clone D1.1, 10 μ g/ml ConA stimulated 15 h (T206); TH2
 - 20 T cell clone CDC35, resting for 3 weeks after last stimulation with antigen (T207); TH2 T cell clone CDC35, 10 μ g/ml ConA stimulated 15 h (T208); Mel14+ naive T cells from spleen, resting (T209); Mel14+ T cells, polarized to Th1 with IFN- γ /IL-12/anti-IL-4 for 6, 12, 24 h pooled
 - 25 (T210); Mel14+ T cells, polarized to Th2 with IL-4/anti-IFN- γ for 6, 13, 24 h pooled (T211); unstimulated mature B cell leukemia cell line A20 (B200); unstimulated B cell line CH12 (B201); unstimulated large B cells from spleen (B202); B cells from total spleen, LPS activated (B203);
 - 30 metrizamide enriched dendritic cells from spleen, resting (D200); dendritic cells from bone marrow, resting (D201); monocyte cell line RAW 264.7 activated with LPS 4 h (M200); bone-marrow macrophages derived with GM and M-CSF (M201); macrophage cell line J774, resting (M202);
 - 35 macrophage cell line J774 + LPS + anti-IL-10 at 0.5, 1, 3, 6, 12 h pooled (M203); macrophage cell line J774 + LPS +

IL-10 at 0.5, 1, 3, 5, 12 h pooled (M204); aerosol challenged mouse lung tissue, Th2 primers, aerosol OVA challenge 7, 14, 23 h pooled (see Garlisi, et al. (1995) Clinical Immunology and Immunopathology 75:75-83; X206);

5 Nippostrongylus-infected lung tissue (see Coffman, et al. (1989) Science 245:308-310; X200); total adult lung, normal (O200); total lung, rag-1 (see Schwarz, et al. (1993) Immunodeficiency 4:249-252; O205); IL-10 K.O. spleen (see Kuhn, et al. (1991) Cell 75:263-274; X201);

10 total adult spleen, normal (O201); total spleen, rag-1 (O207); IL-10 K.O. Peyer's patches (O202); total Peyer's patches, normal (O210); IL-10 K.O. mesenteric lymph nodes (X203); total mesenteric lymph nodes, normal (O211); IL-10 K.O. colon (X203); total colon, normal (O212); NOD

15 mouse pancreas (see Makino, et al. (1980) Jikken Dobutsu 29:1-13; X205); total thymus, rag-1 (O208); total kidney, rag-1 (O209); total heart, rag-1 (O202); total brain, rag-1 (O203); total testes, rag-1 (O204); total liver, rag-1 (O206); rat normal joint tissue (O300); and rat arthritic

20 joint tissue (X300).

The DTLR10 has been found to be highly expressed in precursor dendritic cell type 2 (pDC2). See, e.g., Rissoan, et al. (1999) Science 283:1183-1186; and Siegal, et al. (1999) Science 284:1835-1837. However, it is not

25 expressed on monocytes. The restricted expression of DTLR10 reinforces the suggestions of a role for the receptor in host immune defense. The pDC2 cells are natural interferon producing cells (NIPC), which produce large amounts of IFN α in response to Herpes simplex virus

30 infection.

V. Cloning of species counterparts of DTLRs

Various strategies are used to obtain species counterparts of these DTLRs, preferably from other

35 primates. One method is by cross hybridization using closely related species DNA probes. It may be useful to go into evolutionarily similar species as intermediate

steps. Another method is by using specific PCR primers based on the identification of blocks of similarity or difference between particular species, e.g., human, genes, e.g., areas of highly conserved or nonconserved
5 polypeptide or nucleotide sequence. Alternatively, antibodies may be used for expression cloning.

VI. Production of mammalian DTLR protein

An appropriate, e.g., GST, fusion construct is
10 engineered for expression, e.g., in *E. coli*. For example, a mouse IGIF pGex plasmid is constructed and transformed into *E. coli*. Freshly transformed cells are grown in LB medium containing 50 µg/ml ampicillin and induced with IPTG (Sigma, St. Louis, MO). After overnight induction,
15 the bacteria are harvested and the pellets containing the DTLR protein are isolated. The pellets are homogenized in TE buffer (50 mM Tris-base pH 8.0, 10 mM EDTA and 2 mM pefabloc) in 2 liters. This material is passed through a microfluidizer (Microfluidics, Newton, MA) three times.
20 The fluidized supernatant is spun down on a Sorvall GS-3 rotor for 1 h at 13,000 rpm. The resulting supernatant containing the DTLR protein is filtered and passed over a glutathione-SEPHAROSE column equilibrated in 50 mM Tris-base pH 8.0. The fractions containing the DTLR-GST fusion
25 protein are pooled and cleaved with thrombin (Enzyme Research Laboratories, Inc., South Bend, IN). The cleaved pool is then passed over a Q-SEPHAROSE column equilibrated in 50 mM Tris-base. Fractions containing DTLR are pooled and diluted in cold distilled H₂O, to lower the
30 conductivity, and passed back over a fresh Q-Sepharose column, alone or in succession with an immunoaffinity antibody column.. Fractions containing the DTLR protein are pooled, aliquoted, and stored in the -70° C freezer.

Comparison of the CD spectrum with DTLR1 protein may
35 suggest that the protein is correctly folded. See Hazuda, et al. (1969) J. Biol. Chem. 264:1689-1693.

VII. Biological Assays with DTLRs

Biological assays will generally be directed to the ligand binding feature of the protein or to the kinase/phosphatase activity of the receptor. The activity will typically be reversible, as are many other enzyme actions, and will mediate phosphatase or phosphorylase activities, which activities are easily measured by standard procedures. See, e.g., Hardie, et al. (eds. 1995) The Protein Kinase FactBook vols. I and II, Academic Press, San Diego, CA; Hanks, et al. (1991) Meth. Enzymol. 200:38-62; Hunter, et al. (1992) Cell 70:375-388; Lewin (1990) Cell 61:743-752; Pines, et al. (1991) Cold Spring Harbor Symp. Quant. Biol. 56:449-463; and Parker, et al. (1993) Nature 363:736-738.

The family of interleukin 1s contains molecules, each of which is an important mediator of inflammatory disease. For a comprehensive review, see Dinarello (1996) "Biologic basis for interleukin-1 in disease" Blood 87:2095-2147. There are suggestions that the various Toll ligands may play important roles in the initiation of disease, particularly inflammatory responses. The finding of novel proteins related to the IL-1 family furthers the identification of molecules that provide the molecular basis for initiation of disease and allow for the development of therapeutic strategies of increased range and efficacy.

VIII. Preparation of antibodies specific for, e.g., DTLR4

Inbred Balb/c mice are immunized intraperitoneally with recombinant forms of the protein, e.g., purified DTLR4 or stable transfected NIH-3T3 cells. Animals are boosted at appropriate time points with protein, with or without additional adjuvant, to further stimulate antibody production. Serum is collected, or hybridomas produced with harvested spleens.

Alternatively, Balb/c mice are immunized with cells transformed with the gene or fragments thereof, either endogenous or exogenous cells, or with isolated membranes enriched for expression of the antigen. Serum is
5 collected at the appropriate time, typically after numerous further administrations. Various gene therapy techniques may be useful, e.g., in producing protein in situ, for generating an immune response.

Monoclonal antibodies may be made. For example,
10 splenocytes are fused with an appropriate fusion partner and hybridomas are selected in growth medium by standard procedures. Hybridoma supernatants are screened for the presence of antibodies which bind to the desired DTLR, e.g., by ELISA or other assay. Antibodies which
15 specifically recognize specific DTLR embodiments may also be selected or prepared.

In another method, synthetic peptides or purified protein are presented to an immune system to generate monoclonal or polyclonal antibodies. See, e.g., Coligan
20 (1991) Current Protocols in Immunology Wiley/Greene; and Harlow and Lane (1989) Antibodies: A Laboratory Manual Cold Spring Harbor Press. In appropriate situations, the binding reagent is either labeled as described above, e.g., fluorescence or otherwise, or immobilized to a
25 substrate for panning methods. Nucleic acids may also be introduced into cells in an animal to produce the antigen, which serves to elicit an immune response. See, e.g., Wang, et al. (1993) Proc. Nat'l. Acad. Sci. 90:4156-4160; Barry, et al. (1994) BioTechniques 16:616-619; and Xiang,
30 et al. (1995) Immunity 2: 129-135.

IX. Production of fusion proteins with, e.g., DTLR5

Various fusion constructs are made with DTLR5. This portion of the gene is fused to an epitope tag, e.g., a
35 FLAG tag, or to a two hybrid system construct. See, e.g., Fields and Song (1989) Nature 340:245-246.

The epitope tag may be used in an expression cloning procedure with detection with anti-FLAG antibodies to detect a binding partner, e.g., ligand for the respective DTLR5. The two hybrid system may also be used to isolate
5 proteins which specifically bind to DTLR5.

X. Chromosomal mapping of DTLRs

Chromosome spreads are prepared. In situ hybridization is performed on chromosome preparations
10 obtained from phytohemagglutinin-stimulated lymphocytes cultured for 72 h. 5-bromodeoxyuridine is added for the final seven hours of culture (60 µg/ml of medium), to ensure a posthybridization chromosomal banding of good quality.

15 An appropriate fragment, e.g., a PCR fragment, amplified with the help of primers on total B cell cDNA template, is cloned into an appropriate vector. The vector is labeled by nick-translation with ³H. The radiolabeled probe is hybridized to metaphase spreads as
20 described in Mattei, et al. (1985) Hum. Genet. 69:327-331.

After coating with nuclear track emulsion (KODAK NTB2), slides are exposed, e.g., for 18 days at 4° C. To avoid any slipping of silver grains during the banding procedure, chromosome spreads are first stained with
25 buffered Giemsa solution and metaphase photographed. R-banding is then performed by the fluorochrome-photolysis-Giemsa (FPG) method and metaphases rephotographed before analysis.

Alternatively, FISH can be performed, as described
30 above. The DTLR genes are located on different chromosomes. DTLR2 and DTLR3 are localized to human chromosome 4; DTLR4 is localized to human chromosome 9, and DTLR5 is localized to human chromosome 1. See Figures 4A-4D.

35

XI. Structure activity relationship

Information on the criticality of particular residues is determined using standard procedures and analysis. Standard mutagenesis analysis is performed, e.g., by
5 generating many different variants at determined positions, e.g., at the positions identified above, and evaluating biological activities of the variants. This may be performed to the extent of determining positions which modify activity, or to focus on specific positions
10 to determine the residues which can be substituted to either retain, block, or modulate biological activity.

Alternatively, analysis of natural variants can indicate what positions tolerate natural mutations. This may result from populational analysis of variation among
15 individuals, or across strains or species. Samples from selected individuals are analyzed, e.g., by PCR analysis and sequencing. This allows evaluation of population polymorphisms.

20 XI. Isolation of a ligand for a DTLR

A DTLR can be used as a specific binding reagent to identify its binding partner, by taking advantage of its specificity of binding, much like an antibody would be used. A binding reagent is either labeled as described
25 above, e.g., fluorescence or otherwise, or immobilized to a substrate for panning methods.

The binding composition is used to screen an expression library made from a cell line which expresses a binding partner, i.e., ligand, preferably membrane
30 associated. Standard staining techniques are used to detect or sort surface expressed ligand, or surface expressing transformed cells are screened by panning. Screening of intracellular expression is performed by various staining or immunofluorescence procedures. See
35 also McMahan, et al. (1991) EMBO J. 10:2821-2832.

For example, on day 0, precoat 2-chamber permanox slides with 1 ml per chamber of fibronectin, 10 ng/ml in PBS, for 30 min at room temperature. Rinse once with PBS. Then plate COS cells at $2-3 \times 10^5$ cells per chamber in 1.5 ml of growth media. Incubate overnight at 37° C.

On day 1 for each sample, prepare 0.5 ml of a solution of 66 µg/ml DEAE-dextran, 66 µM chloroquine, and 4 µg DNA in serum free DME. For each set, a positive control is prepared, e.g., of DTLR-FLAG cDNA at 1 and 1/200 dilution, and a negative mock. Rinse cells with serum free DME. Add the DNA solution and incubate 5 hr at 37° C. Remove the medium and add 0.5 ml 10% DMSO in DME for 2.5 min. Remove and wash once with DME. Add 1.5 ml growth medium and incubate overnight.

On day 2, change the medium. On days 3 or 4, the cells are fixed and stained. Rinse the cells twice with Hank's Buffered Saline Solution (HBSS) and fix in 4% paraformaldehyde (PFA)/glucose for 5 min. Wash 3X with HBSS. The slides may be stored at -80° C after all liquid is removed. For each chamber, 0.5 ml incubations are performed as follows. Add HBSS/saponin (0.1%) with 32 µl/ml of 1 M NaN_3 for 20 min. Cells are then washed with HBSS/saponin 1X. Add appropriate DTLR or DTLR/antibody complex to cells and incubate for 30 min. Wash cells twice with HBSS/saponin. If appropriate, add first antibody for 30 min. Add second antibody, e.g., Vector anti-mouse antibody, at 1/200 dilution, and incubate for 30 min. Prepare ELISA solution, e.g., Vector Elite ABC horseradish peroxidase solution, and preincubate for 30 min. Use, e.g., 1 drop of solution A (avidin) and 1 drop solution B (biotin) per 2.5 ml HBSS/saponin. Wash cells twice with HBSS/saponin. Add ABC HRP solution and incubate for 30 min. Wash cells twice with HBSS, second wash for 2 min, which closes cells. Then add Vector diaminobenzoic acid (DAB) for 5 to 10 min. Use 2 drops of buffer plus 4 drops DAB plus 2 drops of H_2O_2 per 5 ml of

glass distilled water. Carefully remove chamber and rinse slide in water. Air dry for a few minutes, then add 1 drop of Crystal Mount and a cover slip. Bake for 5 min at 85-90° C.

- 5 Evaluate positive staining of pools and progressively subclone to isolation of single genes responsible for the binding.

Alternatively, DTLR reagents are used to affinity purify or sort out cells expressing a putative ligand.

- 10 See, e.g., Sambrook, et al. or Ausubel, et al.

- Another strategy is to screen for a membrane bound receptor by panning. The receptor cDNA is constructed as described above. The ligand can be immobilized and used to immobilize expressing cells. Immobilization may be achieved by use of appropriate antibodies which recognize, e.g., a FLAG sequence of a DTLR fusion construct, or by use of antibodies raised against the first antibodies. Recursive cycles of selection and amplification lead to enrichment of appropriate clones and eventual isolation of receptor expressing clones.
- 15
- 20

Phage expression libraries can be screened by mammalian DTLRs. Appropriate label techniques, e.g., anti-FLAG antibodies, will allow specific labeling of appropriate clones.

25

All citations herein are incorporated herein by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

- 30 Many modifications and variations of this invention can be made without departing from its spirit and scope, as will be apparent to those skilled in the art. The specific embodiments described herein are offered by way of example only, and the invention is to be limited by the terms of the appended claims, along with the full scope of
- 35 equivalents to which such claims are entitled; and the

invention is not to be limited by the specific embodiments that have been presented herein by way of example.

- 5 Humans have two distinct types of dendritic cell (DC) precursors. Peripheral blood monocytes (pDC1) give rise to immature myeloid DCs after culturing with GM-CSF and IL-4. These immature cells become mature myeloid DCs (DC1) after stimulation with CD40 ligand (CD40L). The CD4+CD3-
10 CD11c- plasmacytoid cells (pDC2) from blood or tonsils give rise to a distinct type of immature DC after culture with IL-3, and differentiate into mature DCs (DC2) after CD40L stimulation. Rissoan, et al. (1999) Science 283:1183-1186.
- 15 Siegal, et al. (1999) Science 284:1835-1837, show that pDC2 is the "Natural Interferon Producing Cell" (NIPC). Interferons (IFNs) are the most important cytokines in antiviral immune responses. "Natural IFN-producing cells" (NIPCs) in human blood express CD4 and
20 major histocompatibility complex class II proteins, but have not been isolated and further characterized because of their rarity, rapid apoptosis, and lack of lineage markers. Purified NIPCs are here shown to be the CD4(+)CD11c- type 2 dendritic cell precursors (pDC2s),
25 which produce 200 to 1000 times more IFN than other blood cells after microbial challenge. pDC2s are thus an effector cell type of the immune system, critical for antiviral and antitumor immune responses. They are implicated as important cells in HIV infected patients
- 30 Toll-like receptor (TLR) molecules belong to the IL-1/Toll receptor family. Ligands for TLR2 and TLR4 have been identified, and their functions are related to the host immune response to microbial antigen or injury. Takeuchi, et al. (1999) Immunity 11:443-451; and Noshino, et al. (1999) J. Immunol. 162:3749-3752. The pattern of
35 expression of TLRs seem to be restricted. Muzio, et al. (2000) J. Immunol. 164:5998-6004. With these findings that: i) TLR10 is highly expressed and restricted in pDC2s, and ii) pDC2 is the NIPC, it is likely that TLR10
40 will play an important role in the host's innate immune response.

WHAT IS CLAIMED IS:

1. A composition of matter selected from the group consisting of:
- 5 a) a substantially pure or recombinant DTLR2 protein or peptide exhibiting identity over a length of at least about 12 amino acids to SEQ ID NO: 4;
 - b) a natural sequence DTLR2 of SEQ ID NO: 4;
 - c) a fusion protein comprising DTLR2 sequence;
 - 10 d) a substantially pure or recombinant DTLR3 protein or peptide exhibiting identity over a length of at least about 12 amino acids to SEQ ID NO: 6;
 - e) a natural sequence DTLR3 of SEQ ID NO: 6;
 - f) a fusion protein comprising DTLR3 sequence;
 - 15 g) a substantially pure or recombinant DTLR4 protein or peptide exhibiting identity over a length of at least about 12 amino acids to SEQ ID NO: 8;
 - h) a natural sequence DTLR4 of SEQ ID NO: 8;
 - i) a fusion protein comprising DTLR4 sequence;
 - 20 j) a substantially pure or recombinant DTLR5 protein or peptide exhibiting identity over a length of at least about 12 amino acids to SEQ ID NO: 10;
 - k) a natural sequence DTLR5 comprising SEQ ID NO: 10;
 - 25 l) a fusion protein comprising DTLR5 sequence;
 - m) a substantially pure or recombinant DTLR6 protein or peptide exhibiting identity over a length of at least about 12 amino acids to SEQ ID NO: 12, 28, or 30;
 - 30 n) a natural sequence DTLR6 comprising SEQ ID NO: 12, 28, or 30;
 - o) a fusion protein comprising DTLR6 sequence;
 - p) a substantially pure or recombinant DTLR7 protein or peptide exhibiting identity over a length of
 - 35 at least about 12 amino acids to SEQ ID NO: 16, 18, or 37;

- q) a natural sequence DTLR7 comprising SEQ ID NO: 16, 18, or 37;
- r) a fusion protein comprising DTLR7 sequence;
- s) a substantially pure or recombinant DTLR8 protein or peptide exhibiting identity over a length of at least about 12 amino acids to SEQ ID NO: 32 or 39;
- t) a natural sequence DTLR8 comprising SEQ ID NO: 32 or 39;
- u) a fusion protein comprising DTLR8 sequence;
- v) a substantially pure or recombinant DTLR9 protein or peptide exhibiting identity over a length of at least about 12 amino acids to SEQ ID NO: 22 or 41;
- w) a natural sequence DTLR9 comprising SEQ ID NO: 22 or 41;
- x) a fusion protein comprising DTLR9 sequence;
- y) a substantially pure or recombinant DTLR10 protein or peptide exhibiting identity over a length of at least about 12 amino acids to SEQ ID NO: 34, 43, or 45;
- z) a natural sequence DTLR10 comprising SEQ ID NO: 34, 43, or 45;
- zz) a fusion protein comprising DTLR10 sequence.

25

2. A substantially pure or isolated protein comprising a segment exhibiting sequence identity to a corresponding portion of a:

- a) DTLR2 of Claim 1, and said identity is over at least:
 - a) about 15 amino acids;
 - b) about 19 amino acids; or
 - c) about 25 amino acids;
- b) DTLR3 of Claim 1, and said identity is over at least:
 - a) about 15 amino acids;

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- b) about 19 amino acids; or
- c) about 25 amino acids;
- c) DTLR4 of Claim 1, and said identity is over at least:
 - 5 a) about 15 amino acids;
 - b) about 19 amino acids; or
 - c) about 25 amino acids;
- d) DTLR5 of Claim 1, and said identity is over at least:
 - 10 a) about 15 amino acids;
 - b) about 19 amino acids; or
 - c) about 25 amino acids;
- e) DTLR6 of Claim 1, and said identity is over at least:
 - 15 a) about 15 amino acids;
 - b) about 19 amino acids; or
 - c) about 25 amino acids;
- f) DTLR7 of Claim 1, and said identity is over at least:
 - 20 a) about 15 amino acids;
 - b) about 19 amino acids; or
 - c) about 25 amino acids;
- g) DTLR8 of Claim 1, and said identity is over at least:
 - 25 a) about 15 amino acids;
 - b) about 19 amino acids; or
 - c) about 25 amino acids;
- h) DTLR9 of Claim 1, and said identity is over at least:
 - 30 a) about 15 amino acids;
 - b) about 19 amino acids; or
 - c) about 25 amino acids; or
- i) DTLR10 of Claim 1, and said identity is over at least:
 - 35 a) about 15 amino acids;
 - b) about 19 amino acids; or

c) about 25 amino acids.

3. The composition of matter of Claim 1, wherein said:

- 5 a) DTLR2:
 i) comprises a mature sequence of Table 2; or
 ii) lacks post-translational modification;
- b) DTLR3:
 i) comprises a mature sequence of Table 3; or
10 ii) lacks post-translational modification;
- c) DTLR4:
 i) comprises a mature sequence of Table 4; or
 ii) lacks post-translational modification;
- d) DTLR5:
15 i) comprises a mature sequence of Table 5; or
 ii) lacks post-translational modification;
- e) DTLR6:
 i) comprises a mature sequence of Table 6; or
 ii) lacks post-translational modification;
- 20 f) DTLR7:
 i) comprises a sequence of Table 7; or
 ii) lacks post-translational modification;
- g) DTLR8:
 i) comprises a sequence of Table 8; or
25 ii) lacks post-translational modification;
- h) DTLR9:
 i) comprises a sequence of Table 9; or
 ii) lacks post-translational modification;
- i) DTLR10:
30 i) comprises a sequence of Table 10; or
 ii) lacks post-translational modification; or
- j) protein or peptide:
 i) is from a warm blooded animal selected from
 a mammal, including a primate, such as a
35 human;

- ii) comprises at least one polypeptide segment of SEQ ID NO: 4, 6, 26, 10, 12, 28, 30, 16, 18, 37, 39, 32, 22, 34, 43, or 45;
- iii) exhibits a plurality of said segments of identity;
- iv) is a natural allelic variant of DTLR2, DTLR3, DTLR4, DTLR5, DTLR6, DTLR7, DTLR8, DTLR9, or DTLR10;
- v) has a length at least about 30 amino acids;
- vi) exhibits at least two non-overlapping epitopes which are specific for a primate DTLR2, DTLR3, DTLR4, DTLR5, DTLR6, DTLR7, DTLR8, DTLR9, or DTLR10;
- vii) exhibits sequence identity over a length of at least about 35 amino acids to a primate DTLR2, DTLR3, DTLR4, DTLR5, DTLR6, DTLR7, DTLR8, DTLR9, or DTLR10;
- viii) further exhibits at least two non-overlapping epitopes which are specific for a primate DTLR2, DTLR3, DTLR4, DTLR5, DTLR6, DTLR7, DTLR8, DTLR9, or DTLR10;
- ix) exhibits identity over a length of at least about 20 amino acids to a rodent DTLR6;
- x) is glycosylated;
- xi) has a molecular weight of at least 100 kD with natural glycosylation;
- xii) is a synthetic polypeptide;
- xiii) is attached to a solid substrate;
- xiv) is conjugated to another chemical moiety;
- xv) is a 5-fold or less substitution from natural sequence; or
- xvi) is a deletion or insertion variant from a natural sequence.

4. A composition comprising:

- a) a sterile DTLR2 protein or peptide of Claim 1,

- b) said DTLR2 protein or peptide of Claim 1 and a carrier, wherein said carrier is:
- i) an aqueous compound, including water, saline, and/or buffer; and/or
 - 5 ii) formulated for oral, rectal, nasal, topical, or parenteral administration;
- c) a sterile DTLR3 protein or peptide of Claim 1;
- d) said DTLR3 protein or peptide of Claim 1 and a carrier, wherein said carrier is:
- 10 i) an aqueous compound, including water, saline, and/or buffer; and/or
 - ii) formulated for oral, rectal, nasal, topical, or parenteral administration;
- e) a sterile DTLR4 protein or peptide of Claim 1,
- 15 f) said DTLR4 protein or peptide of Claim 1 and a carrier, wherein said carrier is:
- i) an aqueous compound, including water, saline, and/or buffer; and/or
 - ii) formulated for oral, rectal, nasal, topical, or parenteral administration;
- 20 g) a sterile DTLR5 protein or peptide of Claim 1;
- h) said DTLR5 protein or peptide of Claim 1 and a carrier, wherein said carrier is:
- 25 i) an aqueous compound, including water, saline, and/or buffer; and/or
 - ii) formulated for oral, rectal, nasal, topical, or parenteral administration;
- i) a sterile DTLR6 protein or peptide of Claim 1;
- 30 j) said DTLR6 protein or peptide of Claim 1 and a carrier, wherein said carrier is:
- i) an aqueous compound, including water, saline, and/or buffer; and/or
 - ii) formulated for oral, rectal, nasal, topical, or parenteral administration;
- 35 k) a sterile DTLR7 protein or peptide of Claim 1;

- 1) said DTLR7 protein or peptide of Claim 1 and a carrier, wherein said carrier is:
- i) an aqueous compound, including water, saline, and/or buffer; and/or
 - 5 ii) formulated for oral, rectal, nasal, topical, or parenteral administration;
- m) a sterile DTLR8 protein or peptide of Claim 1;
- n) said DTLR8 protein or peptide of Claim 1 and a carrier, wherein said carrier is:
- 10 i) an aqueous compound, including water, saline, and/or buffer; and/or
 - ii) formulated for oral, rectal, nasal, topical, or parenteral administration;
- o) a sterile DTLR9 protein or peptide of Claim 1;
- 15 p) said DTLR9 protein or peptide of Claim 1 and a carrier, wherein said carrier is:
- i) an aqueous compound, including water, saline, and/or buffer; and/or
 - ii) formulated for oral, rectal, nasal, topical, or parenteral administration;
- 20 q) a sterile DTLR10 protein or peptide of Claim 1;
- r) said DTLR10 protein or peptide of Claim 1 and a carrier, wherein said carrier is:
- 25 i) an aqueous compound, including water, saline, and/or buffer; and/or
 - ii) formulated for oral, rectal, nasal, topical, or parenteral administration;
5. The fusion protein of Claim 1, comprising:
- 30 a) mature protein comprising sequence of Table 2, 3, 4, 5, 6, 7, 8, 9, or 10;
 - b) a detection or purification tag, including a FLAG, His6, or Ig sequence; or
 - 35 c) sequence of another receptor protein.

6. A kit comprising a protein or polypeptide of Claim 1, and:

- a) a compartment comprising said protein or polypeptide; and/or
- 5 b) instructions for use or disposal of reagents in said kit.

7. A binding compound comprising an antigen binding site from an antibody, which specifically binds to a
10 natural DTLR2, DTLR3, DTLR4, DTLR5, DTLR6, DTLR7, DTLR8, DTLR9, or DTLR10 protein of Claim 1, wherein:

- a) said protein is a primate protein;
- b) said binding compound is an Fv, Fab, or Fab2 fragment;
- 15 c) said binding compound is conjugated to another chemical moiety; or
- d) said antibody:
 - i) is raised against a peptide sequence of a mature polypeptide of Table 2, 3, 4, 5, 6,
20 7, 8, 9, or 10;
 - ii) is raised against a mature DTLR2, DTLR3, DTLR4, DTLR5, DTLR6, DTLR7, DTLR8, DTLR9, or DTLR10;
 - iii) is raised to a purified human DTLR2,
25 DTLR3, DTLR4, DTLR5, DTLR6, DTLR7, DTLR8, DTLR9, or DTLR10;
 - iv) is immunoselected;
 - v) is a polyclonal antibody;
 - vi) binds to a denatured DTLR2, DTLR3, DTLR4,
30 DTLR5, DTLR6, DTLR7, DTLR8, DTLR9, or DTLR10;
 - vii) exhibits a Kd to antigen of at least 30 μ M;
 - viii) is attached to a solid substrate,
35 including a bead or plastic membrane;
 - ix) is in a sterile composition; or

x) is detectably labeled, including a radioactive or fluorescent label.

8. A kit comprising said binding compound of Claim 5 7, and:

- a) a compartment comprising said binding compound; and/or
- b) instructions for use or disposal of reagents in said kit.

10

9. A method of:

A) making an antibody of Claim 7, comprising immunizing an immune system with an immunogenic amount of:

15

- a) a primate DTLR2;
- b) a primate DTLR3;
- c) a primate DTLR4;
- d) a primate DTLR5;
- e) a primate DTLR6;
- 20 f) a primate DTLR7;
- g) a primate DTLR8;
- h) a primate DTLR9; or
- i) a primate DTLR10;

thereby causing said antibody to be produced; or

25

B) producing an antigen:antibody complex, comprising contacting an antibody of Claim 7 with:

30

- a) a mammalian DTLR2 protein or peptide;
- b) a mammalian DTLR3 protein or peptide;
- c) a mammalian DTLR4 protein or peptide;
- d) a mammalian DTLR5 protein or peptide;
- e) a mammalian DTLR6 protein or peptide;
- f) a mammalian DTLR7 protein or peptide;
- g) a mammalian DTLR8 protein or peptide;
- h) a mammalian DTLR9 protein or peptide; or
- 35 i) a mammalian DTLR10 protein or peptide;

thereby allowing said complex to form.

10. A composition comprising:
- a) a sterile binding compound of Claim 7, or
 - b) said binding compound of Claim 7 and a carrier,
5 wherein said carrier is:
 - i) an aqueous compound, including water,
saline, and/or buffer; and/or
 - ii) formulated for oral, rectal, nasal,
topical, or parenteral administration.
- 10
11. An isolated or recombinant nucleic acid encoding
a protein or peptide or fusion protein of Claim 1,
wherein:
- a) said DTLR is from a mammal; or
 - 15 b) said nucleic acid:
 - i) encodes an antigenic peptide sequence of
Table 2, 3, 4, 5, 6, 7, 8, 9, or 10;
 - ii) encodes a plurality of antigenic peptide
sequences of Table 2, 3, 4, 5, 6, 7, 8, 9,
20 or 10;
 - iii) exhibits at least about 80% identity to a
natural cDNA encoding said segment;
 - iv) is an expression vector;
 - v) further comprises an origin of replication;
 - 25 vi) is from a natural source;
 - vii) comprises a detectable label;
 - viii) comprises synthetic nucleotide sequence;
 - ix) is less than 6 kb, preferably less than 3
kb;
 - 30 x) is from a mammal, including a primate;
 - xi) comprises a natural full length coding
sequence;
 - xii) is a hybridization probe for a gene
encoding said DTLR;

- xiii) comprises at least 17 contiguous nucleotides from Table 2, 3, 4, 5, 6, 7, 8, 9, or 10;
- xiv) comprises at plurality of nonoverlapping segments of least 17 contiguous nucleotides from Table 2, 3, 4, 5, 6, 7, 8, 9, or 10; or
- xv) is a PCR primer, PCR product, or mutagenesis primer.
12. A cell, tissue, or organ comprising a recombinant nucleic acid of Claim 11.
13. The cell of Claim 12, wherein said cell is:
- a) a prokaryotic cell;
 - b) a eukaryotic cell;
 - c) a bacterial cell;
 - d) a yeast cell;
 - e) an insect cell;
 - f) a mammalian cell;
 - g) a mouse cell;
 - h) a primate cell; or
 - i) a human cell.
14. A kit comprising said nucleic acid of Claim 11, and:
- a) a compartment comprising said nucleic acid;
 - b) a compartment further comprising a primate DTLR2, DTLR3, DTLR4, DTLR5, DTLR6, DTLR7, DTLR8, DTLR9, or DTLR10 protein or polypeptide; and/or
 - c) instructions for use or disposal of reagents in said kit.
15. A method of:

- A) making a polypeptide, comprising expressing said nucleic acid of Claim 11, thereby producing said polypeptide; or
- 5 B) making a duplex nucleic acid, comprising contacting said nucleic acid of Claim 11 with a complementary nucleic acid, thereby allowing said duplex to form.
16. A nucleic acid which:
- 10 a) hybridizes under wash conditions of 30° C and less than 2M salt to SEQ ID NO: 3;
- b) hybridizes under wash conditions of 30° C and less than 2 M salt to SEQ ID NO: 5;
- 15 c) hybridizes under wash conditions of 30° C and less than 2M salt to SEQ ID NO: 25;
- d) hybridizes under wash conditions of 30° C and less than 2 M salt to SEQ ID NO: 9;
- e) hybridizes under wash conditions of 30° C and less than 2M salt to SEQ ID NO: 11, 27, or 29;
- 20 f) hybridizes under wash conditions of 30° C and less than 2 M salt to SEQ ID NO: 15, 17, or 36;
- g) hybridizes under wash conditions of 30° C and less than 2M salt to SEQ ID NO: 31 or 38;
- 25 h) hybridizes under wash conditions of 30° C and less than 2 M salt to SEQ ID NO: 21 or 40;
- i) hybridizes under wash conditions of 30° C and less than 2 M salt to SEQ ID NO: 33, 35, 42, or 44;
- 30 j) exhibits at least about 85% identity over a stretch of at least about 30 nucleotides to a primate DTLR2;
- k) exhibits at least about 85% identity over a stretch of at least about 30 nucleotides to a primate DTLR3;

- 1) exhibits at least about 85% identity over a stretch of at least about 30 nucleotides to a primate DTLR4;
- 5 m) exhibits at least about 85% identity over a stretch of at least about 30 nucleotides to a primate DTLR5;
- n) exhibits at least about 85% identity over a stretch of at least about 30 nucleotides to a primate DTLR6;
- 10 o) exhibits at least about 85% identity over a stretch of at least about 30 nucleotides to a primate DTLR7;
- p) exhibits at least about 85% identity over a stretch of at least about 30 nucleotides to a primate DTLR8;
- 15 q) exhibits at least about 85% identity over a stretch of at least about 30 nucleotides to a primate DTLR9; or
- 20 r) exhibits at least about 85% identity over a stretch of at least about 30 nucleotides to a primate DTLR10.
17. The nucleic acid of Claim 16, wherein:
- 25 a) said wash conditions are at 45° C and/or 500 mM salt; or
- b) said identity is at least 90% and/or said stretch is at least 55 nucleotides.
18. The nucleic acid of Claim 17, wherein:
- 30 a) said wash conditions are at 55° C and/or 150 mM salt; or
- b) said identity is at least 95% and/or said stretch is at least 75 nucleotides.
- 35 19. A method of producing a ligand:receptor complex, comprising contacting:

- 5 a) a substantially pure primate DTLR2, including a recombinant or synthetically produced protein, with candidate Toll ligand;
- b) a substantially pure primate DTLR3, including a recombinant or synthetically produced protein, with candidate Toll ligand;
- 10 c) a substantially pure primate DTLR4, including a recombinant or synthetically produced protein, with candidate Toll ligand;
- d) a substantially pure primate DTLR5, including a recombinant or synthetically produced protein, with candidate Toll ligand;
- 15 e) a substantially pure primate DTLR6, including a recombinant or synthetically produced protein, with candidate Toll ligand;
- f) a substantially pure primate DTLR7, including a recombinant or synthetically produced protein, with candidate Toll ligand;
- 20 g) a substantially pure primate DTLR8, including a recombinant or synthetically produced protein, with candidate Toll ligand;
- h) a substantially pure primate DTLR9, including a recombinant or synthetically produced protein, with candidate Toll ligand;
- 25 i) a substantially pure primate DTLR10, including a recombinant or synthetically produced protein, with candidate Toll ligand;

thereby allowing said complex to form.

- 30 20. A method of modulating physiology or development of a cell or tissue culture cells comprising contacting said cell with an agonist or antagonist of a mammalian DTLR2, DTLR3, DTLR4, DTLR5; DTLR6, DTLR7, DTLR8, DTLR9, or DTLR10.

35

21. The method of Claim 20, wherein said agonist or antagonist is of DTLR10, and said cell is a pDC2 cell.

SEQUENCE SUBMISSION

SEQ ID NO: 1 provides primate DTLR1 nucleotide sequence.
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<110> Schering Corp.

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	His Ser Val Thr Gly Cys Ile Pro Lys Thr Leu Glu Ile Leu Asp Val			430			435					440				
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	Thr	Phe	Ser	Lys	Glu	Gln	Leu	Asp	Ser	Phe	His	Thr	Leu	Lys	Thr	Leu	
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	Glu	Ala	Gly	Gly	Asn	Asn	Phe	Ile	Cys	Ser	Cys	Glu	Phe	Leu	Ser	Phe	
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	Asp	Val	Arg	Leu	Ser	Val	Ser	Glu	Cys	His	Arg	Thr	Ala	Leu	Val	Ser	
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	Cys	His	Arg	Phe	His	Gly	Leu	Trp	Tyr	Met	Lys	Met	Met	Trp	Ala	Trp	
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	Ile	Ile	Asp	Ser	Ile	Glu	Lys	Ser	His	Lys	Thr	Val	Phe	Val	Leu	Ser	
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	Arg Lys Ile Met Asn Thr Lys Thr Tyr Leu Glu Trp Pro Met Asp Glu	
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50	tgg gtc tgg gaa cat ttc tct tca atg gaa aag gaa gac caa tct ctc	2352
	Trp Val Trp Glu His Phe Ser Ser Met Glu Lys Glu Asp Gln Ser Leu	
	750 755 760	
55	aaa ttt tgt ctg gaa gaa agg gac ttt gag gcg ggt gtt ttt gaa cta	2400
	Lys Phe Cys Leu Glu Glu Arg Asp Phe Glu Ala Gly Val Phe Glu Leu	
	765 770 775	
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	Glu Ala Ile Val Asn Ser Ile Lys Arg Ser Arg Lys Ile Ile Phe Val	
	780 785 790 795	
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	Ile Thr His His Leu Leu Lys Asp Pro Leu Cys Lys Arg Phe Lys Val	
	800 805 810	
70	cat cat gca gtt caa caa gct att gaa caa aat ctg gat tcc att ata	2544
	His His Ala Val Gln Gln Ala Ile Glu Gln Asn Leu Asp Ser Ile Ile	

	815	820	825	
5	ttg gtt ttc ctt gag gag att cca gat tat aaa ctg aac cat gca ctc Leu Val Phe Leu Glu Glu Ile Pro Asp Tyr Lys Leu Asn His Ala Leu 830 835 840	2592		
10	tgt ttg cga aga gga atg ttt aaa tct cac tgc atc ttg aac tgg cca Cys Leu Arg Arg Gly Met Phe Lys Ser His Cys Ile Leu Asn Trp Pro 845 850 855	2640		
15	gtt cag aaa gaa cgg ata ggt gcc ttt cgt cat aaa ttg caa gta gca Val Gln Lys Glu Arg Ile Gly Ala Phe Arg His Lys Leu Gln Val Ala 860 865 870 875	2688		
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35	Leu Pro Thr Asn Ile Thr Val Leu Asn Leu Thr His Asn Gln Leu Arg 30 35 40 Arg Leu Pro Ala Ala Asn Phe Thr Arg Tyr Ser Gln Leu Thr Ser Leu 45 50 55			
40	Asp Val Gly Phe Asn Thr Ile Ser Lys Leu Glu Pro Glu Leu Cys Gln 60 65 70 75 Lys Leu Pro Met Leu Lys Val Leu Asn Leu Gln His Asn Glu Leu Ser 80 85 90 Gln Leu Ser Asp Lys Thr Phe Ala Phe Cys Thr Asn Leu Thr Glu Leu 95 100 105			
45	His Leu Met Ser Asn Ser Ile Gln Lys Ile Lys Asn Asn Pro Phe Val 110 115 120 Lys Gln Lys Asn Leu Ile Thr Leu Asp Leu Ser His Asn Gly Leu Ser 125 130 135			
50	Ser Thr Lys Leu Gly Thr Gln Val Gln Leu Glu Asn Leu Gln Glu Leu 140 145 150 155			

Leu Leu Ser Asn Asn Lys Ile Gln Ala Leu Lys Ser Glu Glu Leu Asp
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 5 Ile Phe Ala Asn Ser Ser Leu Lys Lys Leu Glu Leu Ser Ser Asn Gln
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 Ile Lys Glu Phe Ser Pro Gly Cys Phe His Ala Ile Gly Arg Leu Phe
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 10 Gly Leu Phe Leu Asn Asn Val Gln Leu Gly Pro Ser Leu Thr Glu Lys
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 15 Asn Ser Gln Leu Ser Thr Thr Ser Asn Thr Thr Phe Leu Gly Leu Lys
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 Trp Thr Asn Leu Thr Met Leu Asp Leu Ser Tyr Asn Asn Leu Asn Val
 255 260 265
 Val Gly Asn Asp Ser Phe Ala Trp Leu Pro Gln Leu Glu Tyr Phe Phe
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 25 Leu Glu Tyr Asn Asn Ile Gln His Leu Phe Ser His Ser Leu His Gly
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 Leu Phe Asn Val Arg Tyr Leu Asn Leu Lys Arg Ser Phe Thr Lys Gln
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 335 340 345
 Gly Ile Lys Ser Asn Met Phe Thr Gly Leu Ile Asn Leu Lys Tyr Leu
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 365 370 375
 Phe Val Ser Leu Ala His Ser Pro Leu His Ile Leu Asn Leu Thr Lys
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 Gly Gln Glu Trp Arg Gly Leu Glu Asn Ile Phe Glu Ile Tyr Leu Ser
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	460	465	470	475
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10	Leu Glu Lys Leu Glu Ile Leu Asp Leu Gln His Asn Asn Leu Ala Arg	510	515	520
	Leu Trp Lys His Ala Asn Pro Gly Gly Pro Ile Tyr Phe Leu Lys Gly	525	530	535
15	Leu Ser His Leu His Ile Leu Asn Leu Glu Ser Asn Gly Phe Asp Glu	540	545	550
	Ile Pro Val Glu Val Phe Lys Asp Leu Phe Glu Leu Lys Ile Ile Asp	560	565	570
20	Leu Gly Leu Asn Asn Leu Asn Thr Leu Pro Ala Ser Val Phe Asn Asn	575	580	585
25	Gln Val Ser Leu Lys Ser Leu Asn Leu Gln Lys Asn Leu Ile Thr Ser	590	595	600
	Val Glu Lys Lys Val Phe Gly Pro Ala Phe Arg Asn Leu Thr Glu Leu	605	610	615
30	Asp Met Arg Phe Asn Pro Phe Asp Cys Thr Cys Glu Ser Ile Ala Trp	620	625	630
	Phe Val Asn Trp Ile Asn Glu Thr His Thr Asn Ile Pro Glu Leu Ser	640	645	650
35	Ser His Tyr Leu Cys Asn Thr Pro Pro His Tyr His Gly Phe Pro Val	655	660	665
40	Arg Leu Phe Asp Thr Ser Ser Cys Lys Asp Ser Ala Pro Phe Glu Leu	670	675	680
	Phe Phe Met Ile Asn Thr Ser Ile Leu Leu Ile Phe Ile Phe Ile Val	685	690	695
45	Leu Leu Ile His Phe Glu Gly Trp Arg Ile Ser Phe Tyr Trp Asn Val	700	705	710
	Ser Val His Arg Val Leu Gly Phe Lys Glu Ile Asp Arg Gln Thr Glu	720	725	730
50	Gln Phe Glu Tyr Ala Ala Tyr Ile Ile His Ala Tyr Lys Asp Lys Asp	735	740	745
55	Trp Val Trp Glu His Phe Ser Ser Met Glu Lys Glu Asp Gln Ser Leu	750	755	760
	Lys Phe Cys Leu Glu Glu Arg Asp Phe Glu Ala Gly Val Phe Glu Leu	765	770	775

Glu Ala Ile Val Asn Ser Ile Lys Arg Ser Arg Lys Ile Ile Phe Val
 780 785 790 795
 5 Ile Thr His His Leu Leu Lys Asp Pro Leu Cys Lys Arg Phe Lys Val
 800 805 810
 His His Ala Val Gln Gln Ala Ile Glu Gln Asn Leu Asp Ser Ile Ile
 815 820 825
 10 Leu Val Phe Leu Glu Glu Ile Pro Asp Tyr Lys Leu Asn His Ala Leu
 830 835 840
 Cys Leu Arg Arg Gly Met Phe Lys Ser His Cys Ile Leu Asn Trp Pro
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 Lys Asn Leu Asp Leu Ser Phe Asn Pro Leu Arg His Leu Gly Ser Tyr
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 Ser Phe Phe Ser Phe Pro Glu Leu Gln Val Leu Asp Leu Ser Arg Cys
 35 40 45
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 Glu Ile Gln Thr Ile Glu Asp Gly Ala Tyr Gln Ser Leu Ser His Leu
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 Ser Thr Leu Ile Leu Thr Gly Asn Pro Ile Gln Ser Leu Ala Leu Gly
 65 70 75 80
 gcc ttt tct gga cta tca agt tta cag aag ctg gtg gct gtg gag aca 288

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	Asn	Leu	Ala	Ser	Leu	Glu	Asn	Phe	Pro	Ile	Gly	His	Leu	Lys	Thr	Leu	
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10	aaa	gaa	ctt	aat	gtg	gct	cac	aat	ctt	atc	caa	tct	ttc	aaa	tta	cct	384
	Lys	Glu	Leu	Asn	Val	Ala	His	Asn	Leu	Ile	Gln	Ser	Phe	Lys	Leu	Pro	
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	Glu	Tyr	Phe	Ser	Asn	Leu	Thr	Asn	Leu	Glu	His	Leu	Asp	Leu	Ser	Ser	
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	Phe	Ile	Gln	Pro	Gly	Ala	Phe	Lys	Glu	Ile	Arg	Leu	His	Lys	Leu	Thr	
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	Leu	Arg	Asn	Asn	Phe	Asp	Ser	Leu	Asn	Val	Met	Lys	Thr	Cys	Ile	Gln	
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	Gly	Leu	Ala	Gly	Leu	Glu	Val	His	Arg	Leu	Val	Leu	Gly	Glu	Phe	Arg	
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	Asn	Glu	Gly	Asn	Leu	Glu	Lys	Phe	Asp	Lys	Ser	Ala	Leu	Glu	Gly	Leu	
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	Cys	Asn	Leu	Thr	Ile	Glu	Glu	Phe	Arg	Leu	Ala	Tyr	Leu	Asp	Tyr	Tyr	
					245					250					255		
45	ctc	gat	gat	att	att	gac	tta	ttt	aat	tgt	ttg	aca	aat	gtt	tct	tca	816
	Leu	Asp	Asp	Ile	Ile	Asp	Leu	Phe	Asn	Cys	Leu	Thr	Asn	Val	Ser	Ser	
				260					265					270			
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	Phe	Ser	Leu	Val	Ser	Val	Thr	Ile	Glu	Arg	Val	Lys	Asp	Phe	Ser	Tyr	
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	Asn	Phe	Gly	Trp	Gln	His	Leu	Glu	Leu	Val	Asn	Cys	Lys	Phe	Gly	Gln	
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	ttt	ccc	aca	ttg	aaa	ctc	aaa	tct	ctc	aaa	agg	ctt	act	ttc	act	tcc	960
	Phe	Pro	Thr	Leu	Lys	Leu	Lys	Ser	Leu	Lys	Arg	Leu	Thr	Phe	Thr	Ser	
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	Phe Leu Asp Leu Ser Arg Asn Gly Leu Ser Phe Lys Gly Cys Cys Ser	
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15	caa agt gat ttt ggg aca acc agc cta aag tat tta gat ctg agc ttc	1104
	Gln Ser Asp Phe Gly Thr Thr Ser Leu Lys Tyr Leu Asp Leu Ser Phe	
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	Asn Gly Val Ile Thr Met Ser Ser Asn Phe Leu Gly Leu Glu Gln Leu	
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	Glu His Leu Asp Phe Gln His Ser Asn Leu Lys Gln Met Ser Glu Phe	
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	Ser Val Phe Leu Ser Leu Arg Asn Leu Ile Tyr Leu Asp Ile Ser His	
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	Thr His Thr Arg Val Ala Phe Asn Gly Ile Phe Asn Gly Leu Ser Ser	
	420 425 430	
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	Ser Leu Gln Val Leu Asn Met Ser His Asn Asn Phe Phe Ser Leu Asp	
	485 490 495	
60	acg ttt cct tat aag tgt ctg aac tcc ctc cag gtt ctt gat tac agt	1536
	Thr Phe Pro Tyr Lys Cys Leu Asn Ser Leu Gln Val Leu Asp Tyr Ser	
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	Ser Ser Leu Ala Phe Leu Asn Leu Thr Gln Asn Asp Phe Ala Cys Thr	
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10	ggc	atg	cct	gtg	ctg	agt	ttg	aat	atc	acc	tgt	cag	atg	aat	aag	acc	1776
	Gly	Met	Pro	Val	Leu	Ser	Leu	Asn	Ile	Thr	Cys	Gln	Met	Asn	Lys	Thr	
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15	atc	att	ggg	gtg	tcg	gtc	ctc	agt	gtg	ctt	gta	gta	tct	gtt	gta	gca	1824
	Ile	Ile	Gly	Val	Ser	Val	Leu	Ser	Val	Leu	Val	Val	Ser	Val	Val	Ala	
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	Val	Leu	Val	Tyr	Lys	Phe	Tyr	Phe	His	Leu	Met	Leu	Leu	Ala	Gly	Cys	
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	Ile	Lys	Tyr	Gly	Arg	Gly	Glu	Asn	Ile	Tyr	Asp	Ala	Phe	Val	Ile	Tyr	
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	Glu	Glu	Gly	Val	Pro	Pro	Phe	Gln	Leu	Cys	Leu	His	Tyr	Arg	Asp	Phe	
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35	att	ccc	ggg	gtg	gcc	att	gct	gcc	aac	atc	atc	cat	gaa	ggg	ttc	cat	2064
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	Lys	Ser	Arg	Lys	Val	Ile	Val	Val	Val	Ser	Gln	His	Phe	Ile	Gln	Ser	
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	Arg	Trp	Cys	Ile	Phe	Glu	Tyr	Glu	Ile	Ala	Gln	Thr	Trp	Gln	Phe	Leu	
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 Cys Asn Leu Thr Ile Glu Glu Phe Arg Leu Ala Tyr Leu Asp Tyr Tyr

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	Ala	Asp	Ile	Tyr	Cys	Val	Tyr	Pro	Asp	Ser	Phe	Ser	Gly	Val	Ser	Leu	
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	Asp Leu Asn Ser Ala Leu Ile Met Val Val Val Gly Ser Leu Ser Gln	
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	His Lys Leu Ser Gln Gln Ile Leu Lys Lys Glc Lys Glu Lys Lys Lys	
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 5 Asn Gln Leu Leu Ala Pro Asn Pro Asp Val Phe Val Ser Leu Ser Val
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 10 Phe Ile Asn Trp Leu Asn His Thr Asn Val Thr Ile Ala Gly Pro Pro
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 30 Thr Glu Pro Asp Met Tyr Lys Tyr Asp Ala Tyr Leu Cys Phe Ser Ser
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 Homo sapiens

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 Ile Ser Lys Leu Leu Gly Ala Arg Trp Phe Pro Lys Thr Leu Pro Cys
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 15 20 25

35 gac aag cat ttg aca gaa att cct gga ggt att ccc acg aac acc acg 192
 Asp Lys His Leu Thr Glu Ile Pro Gly Gly Ile Pro Thr Asn Thr Thr
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 Val Pro Ile Pro Leu Gly Ser Lys Asn Asn Met Cys Ile Lys Arg Leu
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 Gln Ile Lys Pro Arg Ser Phe Ser Gly Leu Thr Tyr Leu Lys Ser Leu
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 Tyr Leu Asp Gly Asn Gln Leu Leu Glu Ile Pro Gln Gly Leu Pro Pro
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	190 195 200	
25	gaa cta tat ctc tac aac aac atg att gca aaa atc caa gaa gat gat	720
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			795			800					805				810		
	ctg	act	aac	ctg	att	ctg	ttc	tca	ctt	tcc	ata	tct	gta	tct	ctc	ttt	2544
	Leu	Thr	Asn	Leu	Ile	Leu	Phe	Ser	Leu	Ser	Ile	Ser	Val	Ser	Leu	Phe	

	815	820	825	
5	ctc atg gtg atg atg aca gca agt cac ctc tat ttc tgg gat gtg tgg Leu Met Val Met Met Thr Ala Ser His Leu Tyr Phe Trp Asp Val Trp 830 835 840	2592		
10	tat att tac cat ttc tgt aag gcc aag ata aag ggg tat cag cgt cta Tyr Ile Tyr His Phe Cys Lys Ala Lys Ile Lys Gly Tyr Gln Arg Leu 845 850 855	2640		
15	ata tca cca gac tgt tgc tat gat gct ttt att gtg tat gac act aaa Ile Ser Pro Asp Cys Cys Tyr Asp Ala Phe Ile Val Tyr Asp Thr Lys 860 865 870	2688		
20	gac cca gct gtg acc gag tgg gtt ttg gct gag ctg gtg gcc aaa ctg Asp Pro Ala Val Thr Glu Trp Val Leu Ala Glu Leu Val Ala Lys Leu 875 880 885 890	2736		
25	gaa gac cca aga gag aaa cat ttt aat tta tgt ctc gag gaa agg gac Glu Asp Pro Arg Glu Lys His Phe Asn Leu Cys Leu Glu Glu Arg Asp 895 900 905	2784		
30	tgg tta cca ggg cag cca gtt ctg gaa aac ctt tcc cag agc ata cag Trp Leu Pro Gly Gln Pro Val Leu Glu Asn Leu Ser Gln Ser Ile Gln 910 915 920	2832		
35	ctt agc aaa aag aca gtg ttt gtg atg aca gac aag tat gca aag act Leu Ser Lys Lys Thr Val Phe Val Met Thr Asp Lys Tyr Ala Lys Thr 925 930 935	2880		
40	gaa aat ttt aag ata gca ttt tac ttg tcc cat cag agg ctc atg gat Glu Asn Phe Lys Ile Ala Phe Tyr Leu Ser His Gln Arg Leu Met Asp 940 945 950	2928		
45	gaa aaa gtt gat gtg att atc ttg ata ttt ctt gag aag ccc ttt cag Glu Lys Val Asp Val Ile Ile Leu Ile Phe Leu Glu Lys Pro Phe Gln 955 960 965 970	2976		
50	aag tcc aag ttc ctc cag ctc cgg aaa agg ctc tgt ggg agt tct gtc Lys Ser Lys Phe Leu Gln Leu Arg Lys Arg Leu Cys Gly Ser Ser Val 975 980 985	3024		
55	ctt gag tgg cca aca aac ccg caa gct cac cca tac ttc tgg cag tgt Leu Glu Trp Pro Thr Asn Pro Gln Ala His Pro Tyr Phe Trp Gln Cys 990 995 1000	3072		
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<213> Unknown

<400> 12

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 -5 -1 1 5 10
 10 Asp Val Thr Leu Asp Val Pro Lys Asn His Val Ile Val Asp Cys Thr
 15 20 25
 Asp Lys His Leu Thr Glu Ile Pro Gly Gly Ile Pro Thr Asn Thr Thr
 30 35 40
 15 Asn Leu Thr Leu Thr Ile Asn His Ile Pro Asp Ile Ser Pro Ala Ser
 45 50 55
 20 Phe His Arg Leu Asp His Leu Val Glu Ile Asp Phe Arg Cys Asn Cys
 60 65 70
 Val Pro Ile Pro Leu Gly Ser Lys Asn Asn Met Cys Ile Lys Arg Leu
 75 80 85 90
 25 Gln Ile Lys Pro Arg Ser Phe Ser Gly Leu Thr Tyr Leu Lys Ser Leu
 95 100 105
 Tyr Leu Asp Gly Asn Gln Leu Leu Glu Ile Pro Gln Gly Leu Pro Pro
 110 115 120
 30 Ser Leu Gln Leu Leu Ser Leu Glu Ala Asn Asn Ile Phe Ser Ile Arg
 125 130 135
 Lys Glu Asn Leu Thr Glu Leu Ala Asn Ile Glu Ile Leu Tyr Leu Gly
 140 145 150
 Gln Asn Cys Tyr Tyr Arg Asn Pro Cys Tyr Val Ser Tyr Ser Ile Glu
 155 160 165 170
 40 Lys Asp Ala Phe Leu Asn Leu Thr Lys Leu Lys Val Leu Ser Leu Lys
 175 180 185
 Asp Asn Asn Val Thr Ala Val Pro Thr Val Leu Pro Ser Thr Leu Thr
 190 195 200
 45 Glu Leu Tyr Leu Tyr Asn Asn Met Ile Ala Lys Ile Gln Glu Asp Asp
 205 210 215
 Phe Asn Asn Leu Asn Gln Leu Gln Ile Leu Asp Leu Ser Gly Asn Cys
 220 225 230
 Pro Arg Cys Tyr Asn Ala Pro Phe Pro Cys Ala Pro Cys Lys Asn Asn
 235 240 245 250
 55 Ser Pro Leu Gln Ile Pro Val Asn Ala Phe Asp Ala Leu Thr Glu Leu
 255 260 265
 Lys Val Leu Arg Leu His Ser Asn Ser Leu Gln His Val Pro Pro Arg

	270	275	280
	Trp Phe Lys Asn Ile Asn Lys Leu Gln Glu Leu Asp Leu Ser Gln Asn		
	285	290	295
5	Phe Leu Ala Lys Glu Ile Gly Asp Ala Lys Phe Leu His Phe Leu Pro		
	300	305	310
10	Ser Leu Ile Gln Leu Asp Leu Ser Phe Asn Phe Glu Leu Gln Val Tyr		
	315	320	325
	Arg Ala Ser Met Asn Leu Ser Gln Ala Phe Ser Ser Leu Lys Ser Leu		
	335	340	345
15	Lys Ile Leu Arg Ile Arg Gly Tyr Val Phe Lys Glu Leu Lys Ser Phe		
	350	355	360
	Asn Leu Ser Pro Leu His Asn Leu Gln Asn Leu Glu Val Leu Asp Leu		
	365	370	375
20	Gly Thr Asn Phe Ile Lys Ile Ala Asn Leu Ser Met Phe Lys Gln Phe		
	380	385	390
25	Lys Arg Leu Lys Val Ile Asp Leu Ser Val Asn Lys Ile Ser Pro Ser		
	395	400	405
	Gly Asp Ser Ser Glu Val Gly Phe Cys Ser Asn Ala Arg Thr Ser Val		
	415	420	425
30	Glu Ser Tyr Glu Pro Gln Val Leu Glu Gln Leu His Tyr Phe Arg Tyr		
	430	435	440
	Asp Lys Tyr Ala Arg Ser Cys Arg Phe Lys Asn Lys Glu Ala Ser Phe		
	445	450	455
35	Met Ser Val Asn Glu Ser Cys Tyr Lys Tyr Gly Gln Thr Leu Asp Leu		
	460	465	470
40	Ser Lys Asn Ser Ile Phe Phe Val Lys Ser Ser Asp Phe Gln His Leu		
	475	480	485
	Ser Phe Leu Lys Cys Leu Asn Leu Ser Gly Asn Leu Ile Ser Gln Thr		
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45	Leu Asn Gly Ser Glu Phe Gln Pro Leu Ala Glu Leu Arg Tyr Leu Asp		
	510	515	520
	Phe Ser Asn Asn Arg Leu Asp Leu Leu His Ser Thr Ala Phe Glu Glu		
	525	530	535
50	Leu His Lys Leu Glu Val Leu Asp Ile Ser Ser Asn Ser His Tyr Phe		
	540	545	550
55	Gln Ser Glu Gly Ile Thr His Met Leu Asn Phe Thr Lys Asn Leu Lys		
	555	560	565
	Val Leu Gln Lys Leu Met Met Asn Asp Asn Asp Ile Ser Ser Ser Thr		
	575	580	585

	Ser Arg Thr Met Glu Ser Glu Ser Leu Arg Thr Leu Glu Phe Arg Gly	
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5	Asn His Leu Asp Val Leu Trp Arg Glu Gly Asp Asn Arg Tyr Leu Gln	
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	Leu Phe Lys Asn Leu Leu Lys Leu Glu Glu Leu Asp Ile Ser Lys Asn	
10	620	625 630
	Ser Leu Ser Phe Leu Pro Ser Gly Val Phe Asp Gly Met Pro Pro Asn	
	635	640 645 650
15	Leu Lys Asn Leu Ser Leu Ala Lys Asn Gly Leu Lys Ser Phe Ser Trp	
	655	660 665
	Lys Lys Leu Gln Cys Leu Lys Asn Leu Glu Thr Leu Asp Leu Ser His	
	670	675 680
20	Asn Gln Leu Thr Thr Val Pro Glu Arg Leu Ser Asn Cys Ser Arg Ser	
	685	690 695
	Leu Lys Asn Leu Ile Leu Lys Asn Asn Gln Ile Arg Ser Leu Thr Lys	
25	700	705 710
	Tyr Phe Leu Gln Asp Ala Phe Gln Leu Arg Tyr Leu Asp Leu Ser Ser	
	715	720 725 730
30	Asn Lys Ile Gln Met Ile Gln Lys Thr Ser Phe Pro Glu Asn Val Leu	
	735	740 745
	Asn Asn Leu Lys Met Leu Leu Leu His His Asn Arg Phe Leu Cys Thr	
	750	755 760
35	Cys Asp Ala Val Trp Phe Val Trp Trp Val Asn His Thr Glu Val Thr	
	765	770 775
	Ile Pro Tyr Leu Ala Thr Asp Val Thr Cys Val Gly Pro Gly Ala His	
40	780	785 790
	Lys Gly Gln Ser Val Ile Ser Leu Asp Leu Tyr Thr Cys Glu Leu Asp	
	795	800 805 810
45	Leu Thr Asn Leu Ile Leu Phe Ser Leu Ser Ile Ser Val Ser Leu Phe	
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	Leu Met Val Met Met Thr Ala Ser His Leu Tyr Phe Trp Asp Val Trp	
	830	835 840
50	Tyr Ile Tyr His Phe Cys Lys Ala Lys Ile Lys Gly Tyr Gln Arg Leu	
	845	850 855
	Ile Ser Pro Asp Cys Cys Tyr Asp Ala Phe Ile Val Tyr Asp Thr Lys	
55	860	865 870
	Asp Pro Ala Val Thr Glu Trp Val Leu Ala Glu Leu Val Ala Lys Leu	
	875	880 885 890

Glu Asp Pro Arg Glu Lys His Phe Asn Leu Cys Leu Glu Glu Arg Asp
 895 900 905
 5 Trp Leu Pro Gly Gln Pro Val Leu Glu Asn Leu Ser Gln Ser Ile Gln
 910 915 920
 Leu Ser Lys Lys Thr Val Phe Val Met Thr Asp Lys Tyr Ala Lys Thr
 925 930 935
 10 Glu Asn Phe Lys Ile Ala Phe Tyr Leu Ser His Gln Arg Leu Met Asp
 940 945 950
 Glu Lys Val Asp Val Ile Ile Leu Ile Phe Leu Glu Lys Pro Phe Gln
 955 960 965 970
 15 Lys Ser Lys Phe Leu Gln Leu Arg Lys Arg Leu Cys Gly Ser Ser Val
 975 980 985
 20 Leu Glu Trp Pro Thr Asn Pro Gln Ala His Pro Tyr Phe Trp Gln Cys
 990 995 1000
 Leu Lys Asn Ala Leu Ala Thr Asp Asn His Val Ala Tyr Ser Gln Val
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 25 Phe Lys Glu Thr Val
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 30 <211> 180
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 35 <223> Description of Unknown Organism: rodent; surmised
 Mus musculus
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 Leu Gly Lys Pro Leu Gln Lys Ser Lys Phe Leu Gln Leu Arg Lys Arg
 45 1 5 10 15
 ctc tgc agg agc tct gtc ctt gag tgg cct gca aat cca cag gct cac 96
 Leu Cys Arg Ser Ser Val Leu Glu Trp Pro Ala Asn Pro Gln Ala His
 20 25 30
 50 cca tac ttc tgg cag tgc ctg aaa aat gcc ctg acc aca gac aat cat 144
 Pro Tyr Phe Trp Gln Cys Leu Lys Asn Ala Leu Thr Thr Asp Asn His
 35 40 45
 55 gtg gct tat agt caa atg ttc aag gaa aca gtc tag 180
 Val Ala Tyr Ser Gln Met Phe Lys Glu Thr Val
 50 55

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 <211> 59
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 5 <213> Unknown

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 10 Leu Cys Arg Ser Ser Val Leu Glu Trp Pro Ala Asn Pro Gln Ala His
 20 25 30
 15 Pro Tyr Phe Trp Gln Cys Leu Lys Asn Ala Leu Thr Thr Asp Asn His
 35 40 45
 Val Ala Tyr Ser Gln Met Phe Lys Glu Thr Val
 50 55
 20
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 Homo sapiens
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 1 5 10 15
 tat ttt aac aaa gtt tgc gag aaa act aac ata gaa gat gga gta ttt 97
 40 Tyr Phe Asn Lys Val Cys Glu Lys Thr Asn Ile Glu Asp Gly Val Phe
 20 25 30
 gaa acg ctg aca aat ttg gag ttg cta tca cta tct ttc aat tct ctt 145
 45 Glu Thr Leu Thr Asn Leu Glu Leu Leu Ser Leu Ser Phe Asn Ser Leu
 35 40 45
 tca cat gtg cca ccc aaa ctg cca agc tcc cta cgc aaa ctt ttt ctg 193
 Ser His Val Pro Pro Lys Leu Pro Ser Ser Leu Arg Lys Leu Phe Leu
 50 55 60
 50 agc aac acc cag atc aaa tac att agt gaa gaa gat ttc aag gga ttg 241
 Ser Asn Thr Gln Ile Lys Tyr Ile Ser Glu Glu Asp Phe Lys Gly Leu
 65 70 75 80
 55 ata aat tta aca tta cta gat tta agc ggg aac tgt ccg agg tgc ttc 289
 Ile Asn Leu Thr Leu Leu Asp Leu Ser Gly Asn Cys Pro Arg Cys Phe
 85 90 95

	aat gcc cca ttt cca tgc gtg cct tgt gat ggt ggt gct tca att aat	337
	Asn Ala Pro Phe Pro Cys Val Pro Cys Asp Gly Gly Ala Ser Ile Asn	
	100 105 110	
5	ata gat cgt ttt gct ttt caa aac ttg acc caa ctt cga tac cta aac	385
	Ile Asp Arg Phe Ala Phe Gln Asn Leu Thr Gln Leu Arg Tyr Leu Asn	
	115 120 125	
10	ctc tct agc act tcc ctc agg aag att aat gct gcc tgg ttt aaa aat	433
	Leu Ser Ser Thr Ser Leu Arg Lys Ile Asn Ala Ala Trp Phe Lys Asn	
	130 135 140	
15	atg cct cat ctg aag gtg ctg gat ctt gaa ttc aac tat tta gtg gga	481
	Met Pro His Leu Lys Val Leu Asp Leu Glu Phe Asn Tyr Leu Val Gly	
	145 150 155 160	
20	gaa ata gcc tct ggg gca ttt tta acg atg ctg ccc cgc tta gaa ata	529
	Glu Ile Ala Ser Gly Ala Phe Leu Thr Met Leu Pro Arg Leu Glu Ile	
	165 170 175	
	ctt gac ttg tct ttt aac tat ata aag ggg agt tat cca cag cat att	577
	Leu Asp Leu Ser Phe Asn Tyr Ile Lys Gly Ser Tyr Pro Gln His Ile	
	180 185 190	
25	aat att tcc aga aac ttc tct aaa ctt ttg tct cta cgg gca ttg cat	625
	Asn Ile Ser Arg Asn Phe Ser Lys Leu Leu Ser Leu Arg Ala Leu His	
	195 200 205	
30	tta aga ggt tat gtg ttc cag gaa ctc aga gaa gat gat ttc cag ccc	673
	Leu Arg Gly Tyr Val Phe Gln Glu Leu Arg Glu Asp Asp Phe Gln Pro	
	210 215 220	
35	ctg atg cag ctt cca aac tta tgc act atc aac ttg ggt att aat ttt	721
	Leu Met Gln Leu Pro Asn Leu Ser Thr Ile Asn Leu Gly Ile Asn Phe	
	225 230 235 240	
40	att aag caa atc gat ttc aaa ctt ttc caa aat ttc tcc aat ctg gaa	769
	Ile Lys Gln Ile Asp Phe Lys Leu Phe Gln Asn Phe Ser Asn Leu Glu	
	245 250 255	
	att att tac ttg tca gaa aac aga ata tca ccg ttg gta aaa gat acc	817
	Ile Ile Tyr Leu Ser Glu Asn Arg Ile Ser Pro Leu Val Lys Asp Thr	
	260 265 270	
45	cgg cag agt tat gca aat agt tcc tct ttt caa cgt cat atc cgg aaa	865
	Arg Gln Ser Tyr Ala Asn Ser Ser Ser Phe Gln Arg His Ile Arg Lys	
	275 280 285	
50	cga cgc tca aca gat ttt gag ttt gac cca cat tgc aac ttt tat cat	913
	Arg Arg Ser Thr Asp Phe Glu Phe Asp Pro His Ser Asn Phe Tyr His	
	290 295 300	
55	ttc acc cgt cct tta ata aag cca caa tgt gct gct tat gga aaa gcc	961
	Phe Thr Arg Pro Leu Ile Lys Pro Gln Cys Ala Ala Tyr Gly Lys Ala	
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	tta gat tta agc ctc aac agt att ttc tt	990
	Leu Asp Leu Ser Leu Asn Ser Ile Phe	

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 15 Glu Thr Leu Thr Asn Leu Glu Leu Leu Ser Leu Ser Phe Asn Ser Leu
 35 40 45

 Ser His Val Pro Pro Lys Leu Pro Ser Ser Leu Arg Lys Leu Phe Leu
 50 55 60
 20 Ser Asn Thr Gln Ile Lys Tyr Ile Ser Glu Glu Asp Phe Lys Gly Leu
 65 70 75 80

 Ile Asn Leu Thr Leu Leu Asp Leu Ser Gly Asn Cys Pro Arg Cys Phe
 85 90 95
 25 Asn Ala Pro Phe Pro Cys Val Pro Cys Asp Gly Gly Ala Ser Ile Asn
 100 105 110
 30 Ile Asp Arg Phe Ala Phe Gln Asn Leu Thr Gln Leu Arg Tyr Leu Asn
 115 120 125

 Leu Ser Ser Thr Ser Leu Arg Lys Ile Asn Ala Ala Trp Phe Lys Asn
 130 135 140
 35 Met Pro His Leu Lys Val Leu Asp Leu Glu Phe Asn Tyr Leu Val Gly
 145 150 155 160

 Glu Ile Ala Ser Gly Ala Phe Leu Thr Met Leu Pro Arg Leu Glu Ile
 165 170 175
 40 Leu Asp Leu Ser Phe Asn Tyr Ile Lys Gly Ser Tyr Pro Gln His Ile
 180 185 190
 45 Asn Ile Ser Arg Asn Phe Ser Lys Leu Leu Ser Leu Arg Ala Leu His
 195 200 205

 Leu Arg Gly Tyr Val Phe Gln Glu Leu Arg Glu Asp Asp Phe Gln Pro
 210 215 220
 50 Leu Met Gln Leu Pro Asn Leu Ser Thr Ile Asn Leu Gly Ile Asn Phe
 225 230 235 240

 Ile Lys Gln Ile Asp Phe Lys Leu Phe Gln Asn Phe Ser Asn Leu Glu
 245 250 255
 55 Ile Ile Tyr Leu Ser Glu Asn Arg Ile Ser Pro Leu Val Lys Asp Thr

	260	265	270	
	Arg Gln Ser Tyr Ala Asn Ser Ser Ser Phe Gln Arg His Ile Arg Lys			
	275	280	285	
5	Arg Arg Ser Thr Asp Phe Glu Phe Asp Pro His Ser Asn Phe Tyr His			
	290	295	300	
10	Phe Thr Arg Pro Leu Ile Lys Pro Gln Cys Ala Ala Tyr Gly Lys Ala			
	305	310	315	320
	Leu Asp Leu Ser Leu Asn Ser Ile Phe			
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	1 5 10 15			
40	gac acc aaa gat gcc tct gtt act gac tgg gtg ata aat gag ctg cgc			96
	Asp Thr Lys Asp Ala Ser Val Thr Asp Trp Val Ile Asn Glu Leu Arg			
	20 25 30			
45	tac cac ctt gaa gag agc cga gac aaa aac gtt ctc ctt tgt cta gag			144
	Tyr His Leu Glu Glu Ser Arg Asp Lys Asn Val Leu Leu Cys Leu Glu			
	35 40 45			
50	gag agg gat tgg gac ccg gga ttg gcc atc atc gac aac ctc atg cag			192
	Glu Arg Asp Trp Asp Pro Gly Leu Ala Ile Ile Asp Asn Leu Met Gln			
	50 55 60			
55	agc atc aac caa agc aag aaa aca gta ttt gtt tta acc aaa aaa tat			240
	Ser Ile Asn Gln Ser Lys Lys Thr Val Phe Val Leu Thr Lys Lys Tyr			
	65 70 75 80			
55	gca aaa agc tgg aac ttt aaa aca gct ttt tac ttg gsc ttg cag agg			288
	Ala Lys Ser Trp Asn Phe Lys Thr Ala Phe Tyr Leu Xaa Leu Gln Arg			
	85 90 95			

cta atg ggt gag aac atg gat gtg att ata ttt atc ctg ctg gag cca 336
 Leu Met Gly Glu Asn Met Asp Val Ile Ile Phe Ile Leu Leu Glu Pro
 100 105 110

5 gtg tta cag cat tct ccg tat ttg agg cta cgg cag cgg atc tgt aag 384
 Val Leu Gln His Ser Pro Tyr Leu Arg Leu Arg Gln Arg Ile Cys Lys
 115 120 125

10 agc tcc atc ctc cag tgg cct gac aac ccg aag gca gaa agg ttg ttt 432
 Ser Ser Ile Leu Gln Trp Pro Asp Asn Pro Lys Ala Glu Arg Leu Phe
 130 135 140

15 tgg caa act ctg wga aat gtg gtc ttg act gaa aat gat tca cgg tat 480
 Trp Gln Thr Leu Xaa Asn Val Val Leu Thr Glu Asn Asp Ser Arg Tyr
 145 150 155 160

aac aat atg tat gtc gat tcc att aag caa tac taactgacgt taagtcatga 533
 Asn Asn Met Tyr Val Asp Ser Ile Lys Gln Tyr
 165 170

20 tttcgcgccca taataaagat gcaaaggaat gacatttcng tattagttat ctattgctan 593
 ggtaacnaaa ttantcccaa aaancttang tnggtttnaa aacaacnaca tnttgctggn 653

25 cccacagttt ttgaggggtca ggagtccagg ccagacataa ctgggtcttc tgcttcaggg 713
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30 tncatgtggt tgttttctgg attcaattcc tcctgggcta ttggccaaag gctatactca 833
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40 tcagttggtc atcaactatt ttcccttgac tgctgtcctg ggatggccgg ctatcttgat 1133
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 35 40 45
 Glu Arg Asp Trp Asp Pro Gly Leu Ala Ile Ile Asp Asn Leu Met Gln
 50 55 60
 Ser Ile Asn Gln Ser Lys Lys Thr Val Phe Val Leu Thr Lys Lys Tyr
 65 70 75 80
 20 Ala Lys Ser Trp Asn Phe Lys Thr Ala Phe Tyr Leu Xaa Leu Gln Arg
 85 90 95
 Leu Met Gly Glu Asn Met Asp Val Ile Ile Phe Ile Leu Leu Glu Pro
 100 105 110
 Val Leu Gln His Ser Pro Tyr Leu Arg Leu Arg Gln Arg Ile Cys Lys
 115 120 125
 30 Ser Ser Ile Leu Gln Trp Pro Asp Asn Pro Lys Ala Glu Arg Leu Phe
 130 135 140
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40 <210> 19
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45 <220>
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 Homo sapiens

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55 <220>
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 <222> (48)..(75)
 <223> Xaa translation depends on genetic code

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      1             5             10             15

5   tgc ctt tat gaa agc tac ttt gac cct ggc aaa agc att agt gaa aat   96
    Cys Leu Tyr Glu Ser Tyr Phe Asp Pro Gly Lys Ser Ile Ser Glu Asn
      20             25             30

10  att gta agc ttc att gag aaa agc tat aag tcc atc ttt gtt ttg tcy   144
    Ile Val Ser Phe Ile Glu Lys Ser Tyr Lys Ser Ile Phe Val Leu Xaa
      35             40             45

15  ccc aac ttt gtc cag aat gag tgg tgc cat tat gaa ttc tac ttt gcc   192
    Pro Asn Phe Val Gln Asn Glu Trp Cys His Tyr Glu Phe Tyr Phe Ala
      50             55             60

20  cac cac aat ctc ttc cat gaa aat tct gat cay ata att ctt atc tta   240
    His His Asn Leu Phe His Glu Asn Ser Asp Xaa Ile Ile Leu Ile Leu
      65             70             75             80

25  ctg gaa ccc att cca ttc tat tgc att ccc acc agg tat cat aaa ctg   288
    Leu Glu Pro Ile Pro Phe Tyr Cys Ile Pro Thr Arg Tyr His Lys Leu
      85             90             95

30  gaa gct ctc ctg gaa aaa aaa gca tac ttg gaa tgg ccc aag gat agg   336
    Glu Ala Leu Leu Glu Lys Lys Ala Tyr Leu Glu Trp Pro Lys Asp Arg
      100            105            110

35  cgt aaa tgt ggg ctt ttc tgg gca aac ctt cga gct gct gtt aat gtt   384
    Arg Lys Cys Gly Leu Phe Trp Ala Asn Leu Arg Ala Ala Val Asn Val
      115            120            125

40  aat gta tta gcc acc aga gaa atg tat gaa ctg cag aca ttc aca gag   432
    Asn Val Leu Ala Thr Arg Glu Met Tyr Glu Leu Gln Thr Phe Thr Glu
      130            135            140

45  tta aat gaa gag tct cga ggt tct aca atc tct ctg atg aga aca gac   480
    Leu Asn Glu Glu Ser Arg Gly Ser Thr Ile Ser Leu Met Arg Thr Asp
      145            150            155            160

    tgt cta taaaatccca cagtccttgg gaagttgggg accacataca ctgttgggat   536
    Cys Leu

    gtacattgat acaaccttta tcatggcaat ttgacaatat ttattaaaat aaaaaatggt 596
    tattcccttc aaaaaaaaaa aaaaaaaaaa aaa                               629

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    Cys Leu Tyr Glu Ser Tyr Phe Asp Pro Gly Lys Ser Ile Ser Glu Asn

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	20	25	30	
	Ile Val Ser Phe Ile Glu Lys Ser Tyr Lys Ser Ile Phe Val Leu Xaa			
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5	Pro Asn Phe Val Gln Asn Glu Trp Cys His Tyr Glu Phe Tyr Phe Ala			
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10	His His Asn Leu Phe His Glu Asn Ser Asp Xaa Ile Ile Leu Ile Leu			
	65	70	75	80
	Leu Glu Pro Ile Pro Phe Tyr Cys Ile Pro Thr Arg Tyr His Lys Leu			
	85	90	95	
15	Glu Ala Leu Leu Glu Lys Lys Ala Tyr Leu Glu Trp Pro Lys Asp Arg			
	100	105	110	
	Arg Lys Cys Gly Leu Phe Trp Ala Asn Leu Arg Ala Ala Val Asn Val			
	115	120	125	
20	Asn Val Leu Ala Thr Arg Glu Met Tyr Glu Leu Gln Thr Phe Thr Glu			
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25	Leu Asn Glu Glu Ser Arg Gly Ser Thr Ile Ser Leu Met Arg Thr Asp			
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50	gaa cat gat tct gcc tgg gtg aaa agt gaa ttg gta cct tac cta gaa			96
	Glu His Asp Ser Ala Trp Val Lys Ser Glu Leu Val Pro Tyr Leu Glu			
	20	25	30	
55	aaa gaa gat ata cag att tgt ctt cat gag aga aac ttt gtc cct gcc			144
	Lys Glu Asp Ile Gln Ile Cys Leu His Glu Arg Asn Phe Val Pro Gly			
	35	40	45	
	aag agc att gtg gaa aat atc atc aac tgc att gag aag agt tac aag			192
	Lys Ser Ile Val Glu Asn Ile Ile Asn Cys Ile Glu Lys Ser Tyr Lys			

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	tcc atc ttt gtt ttg tct ccc aac ttt gtc cag agt gag tgg tgc cat			240
	Ser Ile Phe Val Leu Ser Pro Asn Phe Val Gln Ser Glu Trp Cys His			
5	65	70	75	80
	tac gaa ctc tat ttt gcc cat cac aat ctc ttt cat gaa gga tct aat			288
	Tyr Glu Leu Tyr Phe Ala His His Asn Leu Phe His Glu Gly Ser Asn			
10	85	90	95	
	aac tta atc ctc atc tta ctg gaa ccc att cca cag aac agc att ccc			336
	Asn Leu Ile Leu Ile Leu Leu Glu Pro Ile Pro Gln Asn Ser Ile Pro			
	100	105	110	
15	aac aag tac cac aag ctg aag gct ctc atg acg cag cgg act tat ttg			384
	Asn Lys Tyr His Lys Leu Lys Ala Leu Met Thr Gln Arg Thr Tyr Leu			
	115	120	125	
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35	Lys Glu Asp Ile Gln Ile Cys Leu His Glu Arg Asn Phe Val Pro Gly			
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40	Lys Ser Ile Val Glu Asn Ile Ile Asn Cys Ile Glu Lys Ser Tyr Lys			
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	65	70	75	80
45	Tyr Glu Leu Tyr Phe Ala His His Asn Leu Phe His Glu Gly Ser Asn			
	85	90	95	
	Asn Leu Ile Leu Ile Leu Leu Glu Pro Ile Pro Gln Asn Ser Ile Pro			
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50	Asn Lys Tyr His Lys Leu Lys Ala Leu Met Thr Gln Arg Thr Tyr Leu			
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 Gly Xaa Met Arg Met Pro Cys Pro Thr Met Pro Ser Trp Ser Ser Thr
 25 20 25 30
 aaa cgc rga gcg cag tgg cag act ggg tgt aca acg agc ttc ggg ggc 144
 Lys Arg Xaa Ala Gln Trp Gln Thr Gly Cys Thr Thr Ser Phe Gly Gly
 35 40 45
 30 agc tgg agg agt gcc gtg ggc gct ggg cac tcc gcc tgt gcc tgg agg 192
 Ser Trp Arg Ser Ala Val Gly Ala Gly His Ser Ala Cys Ala Trp Arg
 50 55 60
 35 aac gcg act ggc tgc ctg gca aaa ccc tct ttg aga acc tgt ggg cct 240
 Asn Ala Thr Gly Cys Leu Ala Lys Pro Ser Leu Arg Thr Cys Gly Pro
 65 70 75 80
 40 cgg tct atg gca gcc gca aga cgc tgt ttg tgc tgg ccc aca cgg acc 288
 Arg Ser Met Ala Ala Ala Arg Arg Cys Leu Cys Trp Pro Thr Arg Thr
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 45 ggg tca gtg gtc tct tgc gcg cca ktt ntc ctg ctg gcc cag cag cgc 336
 Gly Ser Val Val Ser Cys Ala Pro Xaa Xaa Leu Leu Ala Gln Gln Arg
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 50 ctg ctg gar gac cgc aag gac gtc gtg gtg ctg gtg atc cta ang cct 384
 Leu Leu Xaa Asp Arg Lys Asp Val Val Val Leu Val Ile Leu Xaa Pro
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 Asp Gly Gln Ala Ser Arg Leu Xaa Asp Ala Leu Thr Ser Ala Ser Ala
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 Ala Arg Val Ser Ser Ser Gly Pro Thr Ser Pro Val Val Ala Gln Leu
 145 150 155 160

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 Leu Arg Pro Ala Cys Met Ala Leu Thr Arg Asp Asn His His Phe Tyr
 165 170 175

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 Asn Arg Asn Phe Cys Gln Gly Thr His Gly Arg Ile Ala Val Ser Arg
 180 185 190

10 aat cct gca cgg tgc cac ctc cac aca cac cta aca tat gcc tgc ctg 624
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 35 40 45

Ser Trp Arg Ser Ala Val Gly Ala Gly His Ser Ala Cys Ala Trp Arg
 50 55 60

35 Asn Ala Thr Gly Cys Leu Ala Lys Pro Ser Leu Arg Thr Cys Gly Pro
 65 70 75 80

Arg Ser Met Ala Ala Ala Arg Arg Cys Leu Cys Trp Pro Thr Arg Thr
 85 90 95

40 Gly Ser Val Val Ser Cys Ala Pro Xaa Xaa Leu Leu Ala Gln Gln Arg
 100 105 110

45 Leu Leu Xaa Asp Arg Lys Asp Val Val Val Leu Val Ile Leu Xaa Pro
 115 120 125

Asp Gly Gln Ala Ser Arg Leu Xaa Asp Ala Leu Thr Ser Ala Ser Ala
 130 135 140

50 Ala Arg Val Ser Ser Ser Gly Pro Thr Ser Pro Val Val Ala Gln Leu
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Leu Arg Pro Ala Cys Met Ala Leu Thr Arg Asp Asn His His Phe Tyr
 165 170 175

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 Met Ser Ala
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40 tcg cgc ctg gct ggg act ctg atc cca gcc atg gcc ttc ctc tcc tgc 163
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45 gtg aga cca gaa agc tgg gag ccc tgc gtg gag gtt cct aat att act 211
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50 tat caa tgc atg gag ctg aat ttc tac aaa atc ccc gac aac ctc ccc 259
 Tyr Gln Cys Met Glu Leu Asn Phe Tyr Lys Ile Pro Asp Asn Leu Pro
 15 20 25

55 ttc tca acc aag aac ctg gac ctg agc ttt aat ccc ctg agg cat tta 307
 Phe Ser Thr Lys Asn Leu Asp Leu Ser Phe Asn Pro Leu Arg His Leu
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60 ggc agc tat agc ttc ttc agt ttc cca gaa ctg cag gtg ctg gat tta 355
 Gly Ser Tyr Ser Phe Phe Ser Phe Pro Glu Leu Gln Val Leu Asp Leu
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65 tcc agg tgt gaa atc cag aca att gaa gat ggg gca tat cag agc cta 403
 Ser Arg Cys Glu Ile Gln Thr Ile Glu Asp Gly Ala Tyr Gln Ser Leu

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	Ala	Leu	Gly	Ala	Phe	Ser	Gly	Leu	Ser	Ser	Leu	Gln	Lys	Leu	Val	Ala	
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15	gtg	gag	aca	aat	cta	gca	tct	cta	gag	aac	ttc	ccc	att	gga	cat	ctc	547
	Val	Glu	Thr	Asn	Leu	Ala	Ser	Leu	Glu	Asn	Phe	Pro	Ile	Gly	His	Leu	
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	Lys	Thr	Leu	Lys	Glu	Leu	Asn	Val	Ala	His	Asn	Leu	Ile	Gln	Ser	Phe	
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25	aaa	tta	cct	gag	tat	ttt	tct	aat	ctg	acc	aat	cta	gag	cac	ttg	gac	643
	Lys	Leu	Pro	Glu	Tyr	Phe	Ser	Asn	Leu	Thr	Asn	Leu	Glu	His	Leu	Asp	
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	Leu	Ser	Ser	Asn	Lys	Ile	Gln	Ser	Ile	Tyr	Cys	Thr	Asp	Leu	Arg	Val	
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	Pro	Met	Asn	Phe	Ile	Gln	Pro	Gly	Ala	Phe	Lys	Glu	Ile	Arg	Leu	His	
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	Cys	Ile	Gln	Gly	Leu	Ala	Gly	Leu	Glu	Val	His	Arg	Leu	Val	Leu	Gly	
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	Glu	Phe	Arg	Asn	Glu	Gly	Asn	Leu	Glu	Lys	Phe	Asp	Lys	Ser	Ala	Leu	
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	Glu	Gly	Leu	Cys	Asn	Leu	Thr	Ile	Glu	Glu	Phe	Arg	Leu	Ala	Tyr	Leu	
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65	gac	tac	tac	ctc	gat	gat	att	att	gac	tta	ttt	aat	tgt	ttg	aca	aat	1027
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70	gtt	tct	tca	ttt	tcc	ctg	gtg	agt	gtg	act	att	gaa	agg	gta	aaa	gac	1075
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5	ttt gga cag ttt ccc aca ttg aaa ctc aaa tct ctc aaa agg ctt act	1171
	Phe Gly Gln Phe Pro Thr Leu Lys Leu Lys Ser Leu Lys Arg Leu Thr	
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10	ttc act tcc aac aaa ggt ggg aat gct ttt tca gaa gtt gat cta cca	1219
	Phe Thr Ser Asn Lys Gly Gly Asn Ala Phe Ser Glu Val Asp Leu Pro	
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	ctg agc ttc aat ggt gtt att acc atg agt tca aac ttc ttg ggc tta	1363
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25	gaa caa cta gaa cat ctg gat ttc cag cat tcc aat ttg aaa caa atg	1411
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	Asp Leu Ser Gln Cys Gln Leu Glu Gln Leu Ser Pro Thr Ala Phe Asn	
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	495 500 505	
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	gat tac agt ctc aat cac ata atg act tcc aaa aaa cag gaa cta cag	1795
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5   atc ttc tgg aga cga ctc aga aaa gcc ctg ctg gat ggt aaa tca tgg 2563
    Ile Phe Trp Arg Arg Leu Arg Lys Ala Leu Leu Asp Gly Lys Ser Trp
                785                790                795

    aat cca gaa gga aca gtg ggt aca gga tgc aat tgg cag gaa gca aca 2611
10  Asn Pro Glu Gly Thr Val Gly Thr Gly Cys Asn Trp Gln Glu Ala Thr
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    Ser Ile
15      815

    caacacttgt tcagttaata agtattaaat gctgccacat gtcaggcctt atgctaaggg 2727

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25  gacagagaaa acagaaagag acattgttct tttcctgagt cttttgaatg gaaattgtat 2967

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 45 Asn Ile Thr Tyr Gln Cys Met Glu Leu Asn Phe Tyr Lys Ile Pro Asp
 15 20 25
 Asn Leu Pro Phe Ser Thr Lys Asn Leu Asp Leu Ser Phe Asn Pro Leu
 30 35 40
 Arg His Leu Gly Ser Tyr Ser Phe Phe Ser Phe Pro Glu Leu Gln Val
 45 50 55
 55 Leu Asp Leu Ser Arg Cys Glu Ile Gln Thr Ile Glu Asp Gly Ala Tyr
 60 65 70
 Gln Ser Leu Ser His Leu Ser Thr Leu Ile Leu Thr Gly Asn Pro Ile

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	Gln Ser Leu Ala	Leu Gly Ala Phe Ser	Gly Leu Ser Ser	Leu Gln Lys
		95	100	105
5	Leu Val Ala Val	Glu Thr Asn Leu Ala	Ser Leu Glu Asn	Phe Pro Ile
		110	115	120
	Gly His Leu Lys	Thr Leu Lys Glu Leu	Asn Val Ala His	Asn Leu Ile
10		125	130	135
	Gln Ser Phe Lys	Leu Pro Glu Tyr Phe	Ser Asn Leu Thr	Asn Leu Glu
		140	145	150
15	His Leu Asp Leu	Ser Ser Asn Lys Ile	Gln Ser Ile Tyr	Cys Thr Asp
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	Leu Arg Val Leu	His Gln Met Pro Leu	Leu Asn Leu Ser	Leu Asp Leu
		175	180	185
20	Ser Leu Xaa Pro	Met Asn Phe Ile Gln	Pro Gly Ala Phe	Lys Glu Ile
		190	195	200
	Arg Leu His Lys	Leu Thr Leu Arg Asn	Asn Phe Asp Ser	Leu Asn Val
25		205	210	215
	Met Lys Thr Cys	Ile Gln Gly Leu Ala	Gly Leu Glu Val	His Arg Leu
		220	225	230
30	Val Leu Gly Glu	Phe Arg Asn Glu Gly	Asn Leu Glu Lys	Phe Asp Lys
		235	240	245
	Ser Ala Leu Glu	Gly Leu Cys Asn Leu	Thr Ile Glu Glu	Phe Arg Leu
		255	260	265
35	Ala Tyr Leu Asp	Tyr Tyr Leu Asp Asp	Ile Ile Asp Leu	Phe Asn Cys
		270	275	280
	Leu Thr Asn Val	Ser Ser Phe Ser Leu	Val Ser Val Thr	Ile Glu Arg
40		285	290	295
	Val Lys Asp Phe	Ser Tyr Asn Phe Gly	Trp Gln His Leu	Glu Leu Val
		300	305	310
45	Asn Cys Lys Phe	Gly Gln Phe Pro Thr	Leu Lys Leu Lys	Ser Leu Lys
		315	320	325
	Arg Leu Thr Phe	Thr Ser Asn Lys Gly	Gly Asn Ala Phe	Ser Glu Val
		335	340	345
50	Asp Leu Pro Ser	Leu Glu Phe Leu Asp	Leu Ser Arg Asn	Gly Leu Ser
		350	355	360
	Phe Lys Gly Cys	Cys Ser Gln Ser Asp	Phe Gly Thr Thr	Ser Leu Lys
55		365	370	375
	Tyr Leu Asp Leu	Ser Phe Asn Gly Val	Ile Thr Met Ser	Ser Asn Phe
		380	385	390

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5	Lys Gln Met Ser Glu Phe Ser Val Phe Leu Ser Leu Arg Asn Leu Ile	415	420	425	
	Tyr Leu Asp Ile Ser His Thr His Thr Arg Val Ala Phe Asn Gly Ile	430	435	440	
10	Phe Asn Gly Leu Ser Ser Leu Glu Val Leu Lys Met Ala Gly Asn Ser	445	450	455	
	Phe Gln Glu Asn Phe Leu Pro Asp Ile Phe Thr Glu Leu Arg Asn Leu	460	465	470	
15	Thr Phe Leu Asp Leu Ser Gln Cys Gln Leu Glu Gln Leu Ser Pro Thr	475	480	485	490
	Ala Phe Asn Ser Leu Ser Ser Leu Gln Val Leu Asn Met Ser His Asn	495	500	505	
	Asn Phe Phe Ser Leu Asp Thr Phe Pro Tyr Lys Cys Leu Asn Ser Leu	510	515	520	
25	Gln Val Leu Asp Tyr Ser Leu Asn His Ile Met Thr Ser Lys Lys Gln	525	530	535	
	Glu Leu Gln His Phe Pro Ser Ser Leu Ala Phe Leu Asn Leu Thr Gln	540	545	550	
30	Asn Asp Phe Ala Cys Thr Cys Glu His Gln Ser Phe Leu Gln Trp Ile	555	560	565	570
	Lys Asp Gln Arg Gln Leu Leu Val Glu Val Glu Arg Met Glu Cys Ala	575	580	585	
	Thr Pro Ser Asp Lys Gln Gly Met Pro Val Leu Ser Leu Asn Ile Thr	590	595	600	
40	Cys Gln Met Asn Lys Thr Ile Ile Gly Val Ser Val Leu Ser Val Leu	605	610	615	
	Val Val Ser Val Val Ala Val Leu Val Tyr Lys Phe Tyr Phe His Leu	620	625	630	
45	Met Leu Leu Ala Gly Cys Ile Lys Tyr Gly Arg Gly Glu Asn Ile Tyr	635	640	645	650
	Asp Ala Phe Val Ile Tyr Ser Ser Gln Asp Glu Asp Trp Val Arg Asn	655	660	665	
	Glu Leu Val Lys Asn Leu Glu Glu Gly Val Pro Pro Phe Gln Leu Cys	670	675	680	
55	Leu His Tyr Arg Asp Phe Ile Pro Gly Val Ala Ile Ala Ala Asn Ile	685	690	695	

Ile His Glu Gly Phe His Lys Ser Arg Lys Val Ile Val Val Val Ser
 700 705 710
 5 Gln His Phe Ile Gln Ser Arg Trp Cys Ile Phe Glu Tyr Glu Ile Ala
 715 720 725 730
 Gln Thr Trp Gln Phe Leu Ser Ser Arg Ala Gly Ile Ile Phe Ile Val
 735 740 745
 10 Leu Gln Lys Val Glu Lys Thr Leu Leu Arg Gln Gln Val Glu Leu Tyr
 750 755 760
 Arg Leu Leu Ser Arg Asn Thr Tyr Leu Glu Trp Glu Asp Ser Val Leu
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 15 Gly Arg His Ile Phe Trp Arg Arg Leu Arg Lys Ala Leu Leu Asp Gly
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 50 gtt ctc tca cta aaa gat aac aat gtc aca gct gtc ccc acc act ttg 96
 Val Leu Ser Leu Lys Asp Asn Asn Val Thr Ala Val Pro Thr Thr Leu
 20 25 30
 55 cca cct aat tta cta gag ctc tat ctt tat aac aat atc att aag aaa 144
 Pro Pro Asn Leu Leu Glu Leu Tyr Leu Tyr Asn Asn Ile Ile Lys Lys
 35 40 45
 atc caa gaa aat gat ttc aat aac ctc aat gag ttg caa gtn ctt gac 192
 Ile Gln Glu Asn Asp Phe Asn Asn Leu Asn Glu Leu Gln Xaa Leu Asp

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5	Leu Xaa Gly Asn Cys Pro Arg Cys Xaa Asn Val Pro Tyr Pro Cys Thr			
	65	70	75	80
	ccg tgt gaa aat aat tcc ccc tta cag atc cat gan aat gct ttc aat			288
	Pro Cys Glu Asn Asn Ser Pro Leu Gln Ile His Xaa Asn Ala Phe Asn			
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		20	25	30
	Pro Pro Asn Leu Leu Glu Leu Tyr Leu Tyr Asn Asn Ile Ile Lys Lys			
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30	Ile Gln Glu Asn Asp Phe Asn Asn Leu Asn Glu Leu Gln Xaa Leu Asp			
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	Leu Xaa Gly Asn Cys Pro Arg Cys Xaa Asn Val Pro Tyr Pro Cys Thr			
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	Met	Pro	Pro	Asn	Leu	Lys	Asn	Leu	Ser	Leu	Ala	Lys	Asn	Gly	Leu	Lys	
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10	tct	ttc	ttt	tgg	gac	aga	ctc	cag	tta	ctg	aag	cat	ttg	gaa	att	ttg	144
	Ser	Phe	Phe	Trp	Asp	Arg	Leu	Gln	Leu	Leu	Lys	His	Leu	Glu	Ile	Leu	
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15	gac	ctc	agc	cat	aac	cag	ctg	aca	aaa	gta	cct	gag	aga	ttg	gcc	aac	192
	Asp	Leu	Ser	His	Asn	Gln	Leu	Thr	Lys	Val	Pro	Glu	Arg	Leu	Ala	Asn	
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	Cys	Ser	Lys	Ser	Leu	Thr	Thr	Leu	Ile	Leu	Lys	His	Asn	Gln	Ile	Arg	
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25	caa	ttg	aca	aaa	tat	ttt	cta	gaa	gat	gct	ttg	caa	ttg	cgc	tat	cta	288
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					85					90					95		
30	gac	atc	agt	tca	aat	aaa	atc	cag	gtc	att	cag	aag	act	agc	ttc	cca	336
	Asp	Ile	Ser	Ser	Asn	Lys	Ile	Gln	Val	Ile	Gln	Lys	Thr	Ser	Phe	Pro	
				100					105					110			
35	gaa	aat	gtc	ctc	aac	aat	ctg	gag	atg	ttg	gtt	tta	cat	cac	aat	cgc	384
	Glu	Asn	Val	Leu	Asn	Asn	Leu	Glu	Met	Leu	Val	Leu	His	His	Asn	Arg	
			115				120						125				
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	Phe	Leu	Cys	Asn	Cys	Asp	Ala	Val	Trp	Phe	Val	Trp	Trp	Val	Asn	His	
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	Pro	Gly	Ala	His	Lys	Gly	Gln	Ser	Val	Ile	Ser	Leu	Asp	Leu	Tyr	Thr	
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55	tgt	gag	tta	gat	ctc	aca	aac	ctg	att	ctg	ttc	tca	gtt	tcc	ata	tca	576
	Cys	Glu	Leu	Asp	Leu	Thr	Asn	Leu	Ile	Leu	Phe	Ser	Val	Ser	Ile	Ser	
				180				185						190			
60	tca	gtc	ctc	ttt	ctt	atg	gta	gtt	atg	aca	aca	agt	cac	ctc	ttt	ttc	624
	Ser	Val	Leu	Phe	Leu	Met	Val	Val	Met	Thr	Thr	Ser	His	Leu	Phe	Phe	
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	Trp	Asp	Met	Trp	Tyr	Ile	Tyr	Tyr	Phe	Trp	Lys	Ala	Lys	Ile	Lys	Gly	
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	Tyr	Pro	Ala	Ser	Ala	Ile	Pro	Trp	Ser	Pro	Cys	Tyr	Asp	Ala	Phe	Ile	
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	Val Tyr Asp Thr Lys Asn Ser Ala Val Thr Glu Trp Val Leu Gln Glu	
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	Leu Val Ala Lys Leu Glu Asp Pro Arg Glu Lys His Phe Asn Leu Cys	
	260 265 270	
10	cta gaa gaa aga gac tgg cta cca gga cag cca gtt cta gaa aac ctt	864
	Leu Glu Glu Arg Asp Trp Leu Pro Gly Gln Pro Val Leu Glu Asn Leu	
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15	tcc cag agc ata cag ctc agc aaa aag aca gtg ttt g-g atg aca cag	912
	Ser Gln Ser Ile Gln Leu Ser Lys Lys Thr Val Phe Val Met Thr Gln	
	290 295 300	
20	aaa tat gct aag act gag agt ttt aag atg gca ttt tat ttg tct cat	960
	Lys Tyr Ala Lys Thr Glu Ser Phe Lys Met Ala Phe Tyr Leu Ser His	
	305 310 315 320	
25	cag agg ctc ctg gat gaa aaa gtg gat gtg att atc ttg ata ttc ttg	1008
	Gln Arg Leu Leu Asp Glu Lys Val Asp Val Ile Ile Leu Ile Phe Leu	
	325 330 335	
	gaa aga cct ctt cag aag tct aag ttt ctt cag ctc agg aag aga ctc	1056
	Glu Arg Pro Leu Gln Lys Ser Lys Phe Leu Gln Leu Arg Lys Arg Leu	
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30	tgc agg agc tct gtc ctt gag tgg cct gca aat cca cag gct cac cca	1104
	Cys Arg Ser Ser Val Leu Glu Trp Pro Ala Asn Pro Gln Ala His Pro	
	355 360 365	
35	tac ttc tgg cag tgc ctg aaa aat gcc ctg acc aca gac aat cat gtg	1152
	Tyr Phe Trp Gln Cys Leu Lys Asn Ala Leu Thr Thr Asp Asn His Val	
	370 375 380	
40	gct tat agt caa atg ttc aag gaa aca gtc tagctctctg aagaatgtca	1202
	Ala Tyr Ser Gln Met Phe Lys Glu Thr Val	
	385 390	
45	ccacctagga catgccttgg tacctgaagt tttcataaag gttccataa atgaaggtct	1262
	gaatttttcc taacagttgt catggctcag attggtggga aatcatcaat atatggctaa	1322
	gaaattaaga aggggagact gatagaagat aatttctttc ttcattgtgcc atgctcagtt	1382
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1756

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Ser Phe Phe Trp Asp Arg Leu Gln Leu Leu Lys His Leu Glu Ile Leu
 35 40 45

20 Asp Leu Ser His Asn Gln Leu Thr Lys Val Pro Glu Arg Leu Ala Asn
 50 55 60

Cys Ser Lys Ser Leu Thr Thr Leu Ile Leu Lys His Asn Gln Ile Arg
 65 70 75 80

25 Gln Leu Thr Lys Tyr Phe Leu Glu Asp Ala Leu Gln Leu Arg Tyr Leu
 85 90 95

30 Asp Ile Ser Ser Asn Lys Ile Gln Val Ile Gln Lys Thr Ser Phe Pro
 100 105 110

Glu Asn Val Leu Asn Asn Leu Glu Met Leu Val Leu His His Asn Arg
 115 120 125

35 Phe Leu Cys Asn Cys Asp Ala Val Trp Phe Val Trp Trp Val Asn His
 130 135 140

Thr Asp Val Thr Ile Pro Tyr Leu Ala Thr Asp Val Thr Cys Val Gly
 145 150 155 160

40 Pro Gly Ala His Lys Gly Gln Ser Val Ile Ser Leu Asp Leu Tyr Thr
 165 170 175

45 Cys Glu Leu Asp Leu Thr Asn Leu Ile Leu Phe Ser Val Ser Ile Ser
 180 185 190

Ser Val Leu Phe Leu Met Val Val Met Thr Thr Ser His Leu Phe Phe
 195 200 205

50 Trp Asp Met Trp Tyr Ile Tyr Tyr Phe Trp Lys Ala Lys Ile Lys Gly
 210 215 220

Tyr Pro Ala Ser Ala Ile Pro Trp Ser Pro Cys Tyr Asp Ala Phe Ile
 225 230 235 240

55 Val Tyr Asp Thr Lys Asn Ser Ala Val Thr Glu Trp Val Leu Gln Glu
 245 250 255

Leu Val Ala Lys Leu Glu Asp Pro Arg Glu Lys His Phe Asn Leu Cys
 260 265 270

5 Leu Glu Glu Arg Asp Trp Leu Pro Gly Gln Pro Val Leu Glu Asn Leu
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Ser Gln Ser Ile Gln Leu Ser Lys Lys Thr Val Phe Val Met Thr Gln
 290 295 300

10 Lys Tyr Ala Lys Thr Glu Ser Phe Lys Met Ala Phe Tyr Leu Ser His
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Gln Arg Leu Leu Asp Glu Lys Val Asp Val Ile Ile Leu Ile Phe Leu
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15 Glu Arg Pro Leu Gln Lys Ser Lys Phe Leu Gln Leu Arg Lys Arg Leu
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20 Cys Arg Ser Ser Val Leu Glu Trp Pro Ala Asn Pro Gln Ala His Pro
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 Homo sapiens

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 Gly Trp Ser Asp Ser Tyr Thr Cys Glu Tyr Pro Leu Asn Leu Arg Gly
 20 25 30

act agg tta aaa gac gtt cat ctc cac gaa tta tct tgc aac aca gct 145
 Thr Arg Leu Lys Asp Val His Leu His Glu Leu Ser Cys Asn Thr Ala
 35 40 45

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	Leu Leu Ile Val Thr Ile Val Val Ile Met Leu Val Leu Gly Leu Ala	
	50 55 60	
5	gtg gcc ttc tgc tgt ctc cac ttt gat ctg ccc tgg tat ctc agg atg	241
	Val Ala Phe Cys Cys Leu His Phe Asp Leu Pro Trp Tyr Leu Arg Met	
	65 70 75 80	
10	cta ggt caa tgc aca caa aca tgg cac agg gtt agg aaa aca acc caa	289
	Leu Gly Gln Cys Thr Gln Thr Trp His Arg Val Arg Lys Thr Thr Gln	
	85 90 95	
15	gaa caa ctc aag aga aat gtc cga ttc cac gca ttt att tca tac agt	337
	Glu Gln Leu Lys Arg Asn Val Arg Phe His Ala Phe Ile Ser Tyr Ser	
	100 105 110	
20	gaa cat gat tct ctg tgg gtg aag aat gaa ttg atc ccc aat cta gag	385
	Glu His Asp Ser Leu Trp Val Lys Asn Glu Leu Ile Pro Asn Leu Glu	
	115 120 125	
25	aag gaa gat ggt tct atc ttg att tgc ctt tat gaa agc tac ttt gac	433
	Lys Glu Asp Gly Ser Ile Leu Ile Cys Leu Tyr Glu Ser Tyr Phe Asp	
	130 135 140	
30	cct ggc aaa agc att agt gaa aat att gta agc ttc att gag aaa agc	481
	Pro Gly Lys Ser Ile Ser Glu Asn Ile Val Ser Phe Ile Glu Lys Ser	
	145 150 155 160	
35	tat aag tcc atc ttt gtt ttg tct ccc aac ttt gtc cag aat gag tgg	529
	Tyr Lys Ser Ile Phe Val Leu Ser Pro Asn Phe Val Gln Asn Glu Trp	
	165 170 175	
40	tgc cat tat gaa ttc tac ttt gcc cac cac aat ctc ttc cat gaa aat	577
	Cys His Tyr Glu Phe Tyr Phe Ala His His Asn Leu Phe His Glu Asn	
	180 185 190	
45	tct gat cac ata att ctt atc tta ctg gaa ccc att cca ttc tat tgc	625
	Ser Asp His Ile Ile Leu Ile Leu Leu Glu Pro Ile Pro Phe Tyr Cys	
	195 200 205	
50	att ccc acc agg tat cat aaa ctg raa gct ctc ctg gaa aaa aaa gca	673
	Ile Pro Thr Arg Tyr His Lys Leu Xaa Ala Leu Leu Glu Lys Lys Ala	
	210 215 220	
55	tac ttg gaa tgg ccc aag gat agg cgt aaa tgt ggg ctt tty tgg gca	721
	Tyr Leu Glu Trp Pro Lys Asp Arg Arg Lys Cys Gly Leu Xaa Trp Ala	
	225 230 235 240	
60	aac ctt cga gct gct gtt aat gtt aat gta tta gcc acc aga gaa atg	769
	Asn Leu Arg Ala Ala Val Asn Val Asn Val Leu Ala Thr Arg Glu Met	
	245 250 255	
65	tat gaa ctg cag aca ttc aca gag tta aat gaa gag tct cga ggt tct	817
	Tyr Glu Leu Gln Thr Phe Thr Glu Leu Asn Glu Glu Ser Arg Gly Ser	
	260 265 270	
70	aca atc tyt ctg atg aga aca gac tgt yta taaaatccca cagtccttgg	867

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Thr Ile Xaa Leu Met Arg Thr Asp Cys Xaa
275                               280

5  gaagttgggg accacataca ctgttgggat gtacattgat acaaccttta tgatggcaat 927
   ttgacaatat ttattaaaat aaaaaatggt tattcccttc aaaaaaaaaa aaaaaaaaaa 987
   aaaaaaaaaa aa                                     999

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20 Gly Trp Ser Asp Ser Tyr Thr Cys Glu Tyr Pro Leu Asn Leu Arg Gly
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   Thr Arg Leu Lys Asp Val His Leu His Glu Leu Ser Cys Asn Thr Ala
    35        40        45

25 Leu Leu Ile Val Thr Ile Val Val Ile Met Leu Val Leu Gly Leu Ala
    50        55        60

   Val Ala Phe Cys Cys Leu His Phe Asp Leu Pro Trp Tyr Leu Arg Met
    65        70        75        80

   Leu Gly Gln Cys Thr Gln Thr Trp His Arg Val Arg Lys Thr Thr Gln
    85        90        95

35 Glu Gln Leu Lys Arg Asn Val Arg Phe His Ala Phe Ile Ser Tyr Ser
    100       105       110

   Glu His Asp Ser Leu Trp Val Lys Asn Glu Leu Ile Pro Asn Leu Glu
    115       120       125

40 Lys Glu Asp Gly Ser Ile Leu Ile Cys Leu Tyr Glu Ser Tyr Phe Asp
    130       135       140

   Pro Gly Lys Ser Ile Ser Glu Asn Ile Val Ser Phe Ile Glu Lys Ser
    145       150       155       160

   Tyr Lys Ser Ile Phe Val Leu Ser Pro Asn Phe Val Gln Asn Glu Trp
    165       170       175

50 Cys His Tyr Glu Phe Tyr Phe Ala His His Asn Leu Phe His Glu Asn
    180       185       190

   Ser Asp His Ile Ile Leu Ile Leu Leu Glu Pro Ile Pro Phe Tyr Cys
    195       200       205

55 Ile Pro Thr Arg Tyr His Lys Leu Xaa Ala Leu Leu Glu Lys Lys Ala
    210       215       220

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Tyr Leu Glu Trp Pro Lys Asp Arg Arg Lys Cys Gly Leu Xaa Trp Ala
225                230                235                240

5  Asn Leu Arg Ala Ala Val Asn Val Asn Val Leu Ala Thr Arg Glu Met
    245                250                255

Tyr Glu Leu Gln Thr Phe Thr Glu Leu Asn Glu Glu Ser Arg Gly Ser
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10 Thr Ile Xaa Leu Met Arg Thr Asp Cys Xaa
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15  <211> 1173
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20  <223> Description of Unknown Organism:primate; surmised
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25  <222> (1)..(1008)

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Leu Pro Ala Gly Thr Arg Leu Arg Arg Leu Asp Val Ser Cys Asn Ser
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atc agc ttc gtg gcc ccc ggc ttc ttt tcc aag gcc aag gag ctg cga 96
Ile Ser Phe Val Ala Pro Gly Phe Phe Ser Lys Ala Lys Glu Leu Arg
    20                25                30

40  gag ctc aac ctt agc gcc aac gcc ctc aag aca gtg gac cac tcc tgg 144
Glu Leu Asn Leu Ser Ala Asn Ala Leu Lys Thr Val Asp His Ser Trp
    35                40                45

45  ttt ggg ccc ctg gcg agt gcc ctg caa ata cta gat gta agc gcc aac 192
Phe Gly Pro Leu Ala Ser Ala Leu Gln Ile Leu Asp Val Ser Ala Asn
    50                55                60

    cct ctg cac tgc gcc tgt ggg gcg gcc ttt atg gac ttc ctg ctg gag 240
Pro Leu His Cys Ala Cys Gly Ala Ala Phe Met Asp Phe Leu Leu Glu
    65                70                75                80

    gtg cag gct gcc gtg ccc ggt ctg ccc agc cgg gtg aag tgt ggc agt 288
Val Gln Ala Ala Val Pro Gly Leu Pro Ser Arg Val Lys Cys Gly Ser
55  85                90                95

ccg ggc cag ctc cag ggc ctc agc atc ttt gca cag gac ctg cgc ctc 336
Pro Gly Gln Leu Gln Gly Leu Ser Ile Phe Ala Gln Asp Leu Arg Leu

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	100	105	110	
5	tgc ctg gat gag gcc ctc tcc tgg gac tgt ttc gcc ctc tcc ctg ctg Cys Leu Asp Glu Ala Leu Ser Trp Asp Cys Phe Ala Leu Ser Leu Leu 115 120 125	384		
10	gct gtg gct ctg ggc ctg ggt gtg ccc atg ctg cat cac ctc tgt ggc Ala Val Ala Leu Gly Leu Gly Val Pro Met Leu His His Leu Cys Gly 130 135 140	432		
15	tgg gac ctc tgg tac tgc ttc cac ctg tgc ctg gcc tgg ctt ccc tgg Trp Asp Leu Trp Tyr Cys Phe His Leu Cys Leu Ala Trp Leu Pro Trp 145 150 155 160	480		
20	cgg ggg cgg caa agt ggg cga gat gag gat gcc ctg ccc tac gat gcc Arg Gly Arg Gln Ser Gly Arg Asp Glu Asp Ala Leu Pro Tyr Asp Ala 165 170 175	528		
25	ttc gtg gtc ttc gac aaa acg cag agc gca gtg gca gac tgg gtg tac Phe Val Val Phe Asp Lys Thr Gln Ser Ala Val Ala Asp Trp Val Tyr 180 185 190	576		
30	aac gag ctt cgg ggg cag ctg gag gag tgc cgt ggg cgc tgg gca ctc Asn Glu Leu Arg Gly Gln Leu Glu Glu Cys Arg Gly Arg Trp Ala Leu 195 200 205	624		
35	cgc ctg tgc ctg gag gaa cgc gac tgg ctg cct ggc aaa acc ctc ttt Arg Leu Cys Leu Glu Glu Arg Asp Trp Leu Pro Gly Lys Thr Leu Phe 210 215 220	672		
40	gag aac ctg tgg gcc tcc gtc tat ggc agc cgc aag acg ctg ttt gtg Glu Asn Leu Trp Ala Ser Val Tyr Gly Ser Arg Lys Thr Leu Phe Val 225 230 235 240	720		
45	ctg gcc cac acg gac cgg gtc agt ggt ctc ttg cgc gcc agc ttc ctg Leu Ala His Thr Asp Arg Val Ser Gly Leu Leu Arg Ala Ser Phe Leu 245 250 255	768		
50	ctg gcc cag cag cgc ctg ctg gag gac cgc aag gac gtc gtg gtg ctg Leu Ala Gln Gln Arg Leu Leu Glu Asp Arg Lys Asp Val Val Val Leu 260 265 270	816		
55	gtg atc ctg agc cct gac ggc cgc cgc tcc cgc tac gkg cgg ctg cgc Val Ile Leu Ser Pro Asp Gly Arg Arg Ser Arg Tyr Xaa Arg Leu Arg 275 280 285	864		
60	cag cgc ctc tgc cgc cag agt gtc ctc ctc tgg ccc cac cag ccc agt Gln Arg Leu Cys Arg Gln Ser Val Leu Leu Trp Pro His Gln Pro Ser 290 295 300	912		
65	ggt cag cgc agc ttc tgg gcc cag ctg ggc atg gcc ctg acc agg gac Gly Gln Arg Ser Phe Trp Ala Gln Leu Gly Met Ala Leu Thr Arg Asp 305 310 315 320	960		
70	aac cac cac ttc tat aac cgg aac ttc tgc cag gga ccc acg gcc gaa Asn His His Phe Tyr Asn Arg Asn Phe Cys Gln Gly Pro Thr Ala Glu 325 330 335	1008		

tagccgtgag ccggaatcct gcacggtgcc acctccacac tcacctcacc tctgcctgcc 1068
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 5 ataatgcta ccgaaggcta aaaaaaaaaa aaaaaaaaaa aanna 1173

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 35 40 45
 Phe Gly Pro Leu Ala Ser Ala Leu Gln Ile Leu Asp Val Ser Ala Asn
 50 55 60
 25 Pro Leu His Cys Ala Cys Gly Ala Ala Phe Met Asp Phe Leu Leu Glu
 65 70 75 80
 Val Gln Ala Ala Val Pro Gly Leu Pro Ser Arg Val Lys Cys Gly Ser
 30 85 90 95
 Pro Gly Gln Leu Gln Gly Leu Ser Ile Phe Ala Gln Asp Leu Arg Leu
 100 105 110
 35 Cys Leu Asp Glu Ala Leu Ser Trp Asp Cys Phe Ala Leu Ser Leu Leu
 115 120 125
 Ala Val Ala Leu Gly Leu Gly Val Pro Met Leu His His Leu Cys Gly
 130 135 140
 40 Trp Asp Leu Trp Tyr Cys Phe His Leu Cys Leu Ala Trp Leu Pro Trp
 145 150 155 160
 Arg Gly Arg Gln Ser Gly Arg Asp Glu Asp Ala Leu Pro Tyr Asp Ala
 45 165 170 175
 Phe Val Val Phe Asp Lys Thr Gln Ser Ala Val Ala Asp Trp Val Tyr
 180 185 190
 50 Asn Glu Leu Arg Gly Gln Leu Glu Glu Cys Arg Gly Arg Trp Ala Leu
 195 200 205
 Arg Leu Cys Leu Glu Glu Arg Asp Trp Leu Pro Gly Lys Thr Leu Phe
 210 215 220
 55 Glu Asn Leu Trp Ala Ser Val Tyr Gly Ser Arg Lys Thr Leu Phe Val
 225 230 235 240

Leu Ala His Thr Asp Arg Val Ser Gly Leu Leu Arg Ala Ser Phe Leu
 245 250 255
 5 Leu Ala Gln Gln Arg Leu Leu Glu Asp Arg Lys Asp Val Val Val Leu
 260 265 270
 Val Ile Leu Ser Pro Asp Gly Arg Arg Ser Arg Tyr Xaa Arg Leu Arg
 275 280 285
 10 Gln Arg Leu Cys Arg Gln Ser Val Leu Leu Trp Pro His Gln Pro Ser
 290 295 300
 Gly Gln Arg Ser Phe Trp Ala Gln Leu Gly Met Ala Leu Thr Arg Asp
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 15 Asn His His Phe Tyr Asn Arg Asn Phe Cys Gln Gly Pro Thr Ala Glu
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 35 cgtcccgtta tgtgcgactg cgccagcgtc tctgccgcca gagtgtgctc ttctggcccc 180
 agcgacccaa cgggcagggg ggcttctcgg ccagctgag tacagccctg actagggaca 240
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 40 cagctggaaa cagctgcac ttcattgtctg gttcccgagt tgctctgcct gccttgctct 360
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10 <221> misc_feature
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   gcc gaa gaa aat ttt tct aga agc tat cct tgt gat gag aaa aag caa 96
   Ala Glu Glu Asn Phe Ser Arg Ser Tyr Pro Cys Asp Glu Lys Lys Gln
  20  -1  1                5                10                15

   aat gac tca gtt att gca gag tgc agc aat cgt cga cta cag gaa gtt 144
   Asn Asp Ser Val Ile Ala Glu Cys Ser Asn Arg Arg Leu Gln Glu Val
                        20                25                30

25   ccc caa acg gtg ggc aaa tat gtg aca gaa cta gac ctg tct gat aat 192
   Pro Gln Thr Val Gly Lys Tyr Val Thr Glu Leu Asp Leu Ser Asp Asn
                        35                40                45

30   ttc atc aca cac ata acg aat gaa tca ttt caa ggg ctg caa aat ctc 240
   Phe Ile Thr His Ile Thr Asn Glu Ser Phe Gln Gly Leu Gln Asn Leu
                        50                55                60

35   act aaa ata aat cta aac cac aac ccc aat gta cag cac cag aac gga 288
   Thr Lys Ile Asn Leu Asn His Asn Pro Asn Val Gln His Gln Asn Gly
                        65                70                75

   aat ccc ggt ata caa tca aat ggc ttg aat atc aca gac ggg gca ttc 336
   Asn Pro Gly Ile Gln Ser Asn Gly Leu Asn Ile Thr Asp Gly Ala Phe
  40  80                85                90                95

   ctc aac cta aaa aac cta agg gag tta ctg ctt gaa gac aac cag tta 384
   Leu Asn Leu Lys Asn Leu Arg Glu Leu Leu Leu Glu Asp Asn Gln Leu
                        100               105               110

45   ccc caa ata ccc tct ggt ttg cca gag tct ttg aca gaa ctt agt cta 432
   Pro Gln Ile Pro Ser Gly Leu Pro Glu Ser Leu Thr Glu Leu Ser Leu
                        115               120               125

50   att caa aac aat ata tac aac ata act aaa gag ggc att tca aga ctt 480
   Ile Gln Asn Asn Ile Tyr Asn Ile Thr Lys Glu Gly Ile Ser Arg Leu
                        130               135               140

55   ata aac ttg aaa aat ctc tat ttg gcc tgg aac tgc tat ttt aac aaa 528
   Ile Asn Leu Lys Asn Leu Tyr Leu Ala Trp Asn Cys Tyr Phe Asn Lys
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   gtt tgc gag aaa act aac ata gaa gat gga gta ttt gaa acg ctg aca 576

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	180 185 190	
10	ccc aaa ctg cca agc tcc cta cgc aaa ctt ttt ctg agc aac acc cag Pro Lys Leu Pro Ser Ser Leu Arg Lys Leu Phe Leu Ser Asn Thr Gln	672
	195 200 205	
15	atc aaa tac att agt gaa gaa gat ttc aag gga ttg ata aat tta aca Ile Lys Tyr Ile Ser Glu Glu Asp Phe Lys Gly Leu Ile Asn Leu Thr	720
	210 215 220	
	tta cta gat tta agc ggg aac tgt ccg agg tgc ttc aat gcc cca ttt Leu Leu Asp Leu Ser Gly Asn Cys Pro Arg Cys Phe Asn Ala Pro Phe	768
	225 230 235	
20	cca tgc gtg cct tgt gat ggt ggt gct tca att aat ata gat cgt ttt Pro Cys Val Pro Cys Asp Gly Gly Ala Ser Ile Asn Ile Asp Arg Phe	816
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	260 265 270	
30	tcc ctc agg aag att aat gct gcc tgg ttt aaa aat atg cct cat ctg Ser Leu Arg Lys Ile Asn Ala Ala Trp Phe Lys Asn Met Pro His Leu	912
	275 280 285	
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	290 295 300	
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	320 325 330 335	
45	aac ttc tct aaa ctt ttg tct cta cgg gca ttg cat tta aga ggt tat Asn Phe Ser Lys Leu Leu Ser Leu Arg Ala Leu His Leu Arg Gly Tyr	1104
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	355 360 365	
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	gat ttc aaa ctt ttc caa aat ttc tcc aat ctg gaa att att tac ttg Asp Phe Lys Leu Phe Gln Asn Phe Ser Asn Leu Glu Ile Ile Tyr Leu	1248
	385 390 395	

5	tca gaa aac aga ata tca ccg ttg gta aaa gat acc cgg cag agt tat	1296
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	Asp Phe Glu Phe Asp Pro His Ser Asn Phe Tyr His Phe Thr Arg Pro	
	435 440 445	
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	450 455 460	
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	465 470 475	
30	gac att gcc tgt tta aat ctg tct gca aat agc aat gct caa gtg tta	1536
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	480 485 490 495	
35	agt gga act gaa ttt tca gcc att cct cat gtc aaa tat ttg gat ttg	1584
	Ser Gly Thr Glu Phe Ser Ala Ile Pro His Val Lys Tyr Leu Asp Leu	
	500 505 510	
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	530 535 540	
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	Lys Tyr Asn Leu Glu Ser Lys Ser Leu Val Glu Leu Val Phe Ser Gly	
	580 585 590	
65	aat cgc ctt gac att ttg tgg aat gat gat gac aac agg tat atc tcc	1872
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70	att ttc aaa ggt ctc aag aat ctg aca cgt ctg gat tta tcc ctt aat	1920
	Ile Phe Lys Gly Leu Lys Asn Leu Thr Arg Leu Asp Leu Ser Leu Asn	
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75	agg ctc aag cac atc cca aat gaa gca ttc ctt aat ttg cca gcg agt	1968

	Arg	Leu	Lys	His	Ile	Pro	Asn	Glu	Ala	Phe	Leu	Asn	Leu	Pro	Ala	Ser	
	625						630					635					
5	ctc	act	gaa	cta	cat	ata	aat	gat	aat	atg	tta	aag	ttt	ttt	aac	tgg	2016
	Leu	Thr	Glu	Leu	His	Ile	Asn	Asp	Asn	Met	Leu	Lys	Phe	Phe	Asn	Trp	
	640					645					650					655	
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	Thr	Leu	Leu	Gln	Gln	Phe	Pro	Arg	Leu	Glu	Leu	Leu	Asp	Leu	Arg	Gly	
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15	aac	aaa	cta	ctc	ttt	tta	act	gat	agc	cta	tct	gac	ttt	aca	tct	tcc	2112
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	Leu	Arg	Thr	Leu	Leu	Leu	Ser	His	Asn	Arg	Ile	Ser	His	Leu	Pro	Ser	
				690				695					700				
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	720					725					730					735	
35	acc	aaa	tta	tct	atg	ttg	gaa	cta	cac	gga	aac	ccc	ttt	gaa	tgc	acc	2304
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	Arg	Gly	Lys	Ser	Ile	Val	Ser	Leu	Glu	Leu	Thr	Thr	Cys	Val	Ser	Asp	
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	Val	Thr	Ala	Val	Ile	Leu	Phe	Phe	Phe	Thr	Phe	Phe	Ile	Thr	Thr	Met	
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60	gtt	atg	ttg	gct	gcc	ctg	gct	cac	cat	ttg	ttt	tac	tgg	gat	gtt	tgg	2544
	Val	Met	Leu	Ala	Ala	Leu	Ala	His	His	Leu	Phe	Tyr	Trp	Asp	Val	Trp	
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70	tcc	aca	tcc	caa	act	ttc	tat	gat	gct	tac	att	tct	tat	gac	acc	aaa	2640
	Ser	Thr	Ser	Gln	Thr	Phe	Tyr	Asp	Ala	Tyr	Ile	Ser	Tyr	Asp	Thr	Lys	
			850					855					860				

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	Asp Ala Ser Val Thr Asp Trp Val Ile Asn Glu Leu Arg Tyr His Leu	
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	Glu Glu Ser Arg Asp Lys Asn Val Leu Leu Cys Leu Glu Glu Arg Asp	
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	Trp Asp Pro Gly Leu Ala Ile Ile Asp Asn Leu Met Gln Ser Ile Asn	
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	caa agc aag aaa aca gta ttt gtt tta acc aaa aaa tat gca aaa agc	2832
	Gln Ser Lys Lys Thr Val Phe Val Leu Thr Lys Lys Tyr Ala Lys Ser	
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	Trp Asn Phe Lys Thr Ala Phe Tyr Leu Ala Leu Gln Arg Leu Met Gly	
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	Glu Asn Met Asp Val Ile Ile Phe Ile Leu Leu Glu Pro Val Leu Gln	
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	His Ser Pro Tyr Leu Arg Leu Arg Gln Arg Ile Cys Lys Ser Ser Ile	
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	Leu Gln Trp Pro Asp Asn Pro Lys Ala Glu Gly Leu Phe Trp Gln Thr	
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	Leu Arg Asn Val Val Leu Thr Glu Asn Asp Ser Arg Tyr Asn Asn Met	
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	Ile Gln Asn Asn Ile Tyr Asn Ile Thr Lys Glu Gly Ile Ser Arg Leu		
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25	Val Cys Glu Lys Thr Asn Ile Glu Asp Gly Val Phe Glu Thr Leu Thr		
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	Asn Leu Glu Leu Leu Ser Leu Ser Phe Asn Ser Leu Ser His Val Pro		
	180	185	190
30	Pro Lys Leu Pro Ser Ser Leu Arg Lys Leu Phe Leu Ser Asn Thr Gln		
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	Ile Lys Tyr Ile Ser Glu Glu Asp Phe Lys Gly Leu Ile Asn Leu Thr		
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40	Pro Cys Val Pro Cys Asp Gly Gly Ala Ser Ile Asn Ile Asp Arg Phe		
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	Ala Phe Gln Asn Leu Thr Gln Leu Arg Tyr Leu Asn Leu Ser Ser Thr		
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	Lys Val Leu Asp Leu Glu Phe Asn Tyr Leu Val Gly Glu Ile Ala Ser		
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55	Phe Asn Tyr Ile Lys Gly Ser Tyr Pro Gln His Ile Asn Ile Ser Arg		
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	Asp Phe Glu Phe Asp Pro His Ser Asn Phe Tyr His Phe Thr Arg Pro	435	440	445
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25	Leu Asn Ser Ile Phe Phe Ile Gly Pro Asn Gln Phe Glu Asn Leu Pro	465	470	475
	Asp Ile Ala Cys Leu Asn Leu Ser Ala Asn Ser Asn Ala Gln Val Leu	480	485	490
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	Thr Asn Asn Arg Leu Asp Phe Asp Asn Ala Ser Ala Leu Thr Glu Leu	515	520	525
35	Ser Asp Leu Glu Val Leu Asp Leu Ser Tyr Asn Ser His Tyr Phe Arg	530	535	540
40	Ile Ala Gly Val Thr His His Leu Glu Phe Ile Gln Asn Phe Thr Asn	545	550	555
	Leu Lys Val Leu Asn Leu Ser His Asn Asn Ile Tyr Thr Leu Thr Asp	560	565	570
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	Thr Thr Leu Asp Leu Ser Tyr Asn Leu Leu Phe Gln Leu Gln Ser Ser						
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	Asp Phe His Ser Val Ser Lys Leu Arg Val Leu Ile Leu Cys His Asn						
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	Arg Ile Gln Gln Leu Asp Leu Lys Thr Phe Glu Phe Asn Lys Glu Leu						
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	Arg Tyr Leu Asp Leu Ser Asn Asn Arg Leu Lys Ser Val Thr Trp Tyr	
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	Leu Leu Ala Gly Leu Arg Tyr Leu Asp Leu Ser Phe Asn Asp Phe Asp	
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	Thr Met Pro Ile Cys Glu Glu Ala Gly Asn Met Ser His Leu Glu Ile	
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	Leu Gly Leu Ser Gly Ala Lys Ile Gln Lys Ser Asp Phe Gln Lys Ile	
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	Ala His Leu His Leu Asn Thr Val Phe Leu Gly Phe Arg Thr Leu Pro	
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	His Tyr Glu Glu Gly Ser Leu Pro Ile Leu Asn Thr Thr Lys Leu His	
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	Leu Thr Lys Met Asp Ile Glu Asn Leu Thr Ile Ser Asn Ala Gln Met	
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	Ala Phe Cys Cys Leu His Phe Asp Leu Pro Trp Tyr Leu Arg Met Leu	
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	240	245 250
25	His Phe Gln Ile Arg Asn Val Thr Phe Gly Gly Lys Ala Tyr Leu Asp	
	255	260 265
	His Asn Ser Phe Asp Tyr Ser Asn Thr Val Met Arg Thr Ile Lys Leu	
30	270	275 280 285
	Glu His Val His Phe Arg Val Phe Tyr Ile Gln Gln Asp Lys Ile Tyr	
	290	295 300
35	Leu Leu Leu Thr Lys Met Asp Ile Glu Asn Leu Thr Ile Ser Asn Ala	
	305	310 315
	Gln Met Pro His Met Leu Phe Pro Asn Tyr Pro Thr Lys Phe Gln Tyr	
	320	325 330
40	Leu Asn Phe Ala Asn Asn Ile Leu Thr Asp Glu Leu Phe Lys Arg Thr	
	335	340 345
	Ile Gln Leu Pro His Leu Lys Thr Leu Ile Leu Asn Gly Asn Lys Leu	
45	350	355 360 365
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	370	375 380
50	His Leu Asp Leu Ser Gln Asn Leu Leu Gln His Lys Asn Asp Glu Asn	
	385	390 395
	Cys Ser Trp Pro Glu Thr Val Val Asn Met Asn Leu Ser Tyr Asn Lys	
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55	Leu Ser Asp Ser Val Phe Arg Cys Leu Pro Lys Ser Ile Gln Ile Leu	
	415	420 425

	Asp	Leu	Asn	Asn	Asn	Gln	Ile	Gln	Thr	Val	Pro	Lys	Glu	Thr	Ile	His	430	435	440	445
5	Leu	Met	Ala	Leu	Arg	Glu	Leu	Asn	Ile	Ala	Phe	Asn	Phe	Leu	Thr	Asp	450	455	460	
	Leu	Pro	Gly	Cys	Ser	His	Phe	Ser	Arg	Leu	Ser	Val	Leu	Asn	Ile	Glu	465	470	475	
10	Met	Asn	Phe	Ile	Leu	Ser	Pro	Ser	Leu	Asp	Phe	Val	Gln	Ser	Cys	Gln	480	485	490	
15	Glu	Val	Lys	Thr	Leu	Asn	Ala	Gly	Arg	Asn	Pro	Phe	Arg	Cys	Thr	Cys	495	500	505	
	Glu	Leu	Lys	Asn	Phe	Ile	Gln	Leu	Glu	Thr	Tyr	Ser	Glu	Val	Met	Met	510	515	520	525
20	Val	Gly	Trp	Ser	Asp	Ser	Tyr	Thr	Cys	Glu	Tyr	Pro	Leu	Asn	Leu	Arg	530	535	540	
	Gly	Thr	Arg	Leu	Lys	Asp	Val	His	Leu	His	Glu	Leu	Ser	Cys	Asn	Thr	545	550	555	
25	Ala	Leu	Leu	Ile	Val	Thr	Ile	Val	Val	Ile	Met	Leu	Val	Leu	Gly	Leu	560	565	570	
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35	Gln	Glu	Gln	Leu	Lys	Arg	Asn	Val	Arg	Phe	His	Ala	Phe	Ile	Ser	Tyr	610	615	620	
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	Ser	Tyr	Lys	Ser	Ile	Phe	Val	Leu	Ser	Pro	Asn	Phe	Val	Gln	Asn	Glu	670	675	680	685
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	Asn	Ser	Asp	His	Ile	Ile	Leu	Ile	Leu	Leu	Glu	Pro	Ile	Pro	Phe	Tyr	705	710	715	
55	Cys	Ile	Pro	Thr	Arg	Tyr	His	Lys	Leu	Lys	Ala	Leu	Leu	Glu	Lys	Lys	720	725	730	
	Ala	Tyr	Leu	Glu	Trp	Pro	Lys	Asp	Arg	Arg	Lys	Cys	Gly	Leu	Phe	Trp				

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	Ala Asn Leu Arg	Ala Ala Ile Asn Val	Asn Val Leu Ala Thr Arg Glu	
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5	Met Tyr Glu Leu Gln Thr Phe Thr Glu Leu Asn, Glu Glu Ser Arg Gly	770	775	780
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40	Met Thr Lys Asp Lys Glu Pro Ile Val Lys Ser Phe His Phe	-30 -25 -20		
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	Gly Asn Glu Phe Ala Val Asp Lys Ser Lys Arg Gly Leu Ile His Val	-1 1 5 10 15		
50	cca aaa gac cta ccg ctg aaa acc aaa gtc tta gat atg tct cag aac	253		
	Pro Lys Asp Leu Pro Leu Lys Thr Lys Val Leu Asp Met Ser Gln Asn	20 25 30		
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55	Tyr Ile Ala Glu Leu Gln Val Ser Asp Met Ser Phe Leu Ser Glu Leu	35 40 45		
	aca gtt ttg aga ctt tcc cat aac aga atc cag cta ctt gat tta agt	349		

	Thr	Val	Leu	Arg	Leu	Ser	His	Asn	Arg	Ile	Gln	Leu	Leu	Asp	Leu	Ser	
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	Val	Phe	Lys	Phe	Asn	Gln	Asp	Leu	Glu	Tyr	Leu	Asp	Leu	Ser	His	Asn	
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10	cag	ttg	caa	aag	ata	tcc	tgc	cat	cct	att	gtg	agt	ttc	agg	cat	tta	445
	Gln	Leu	Gln	Lys	Ile	Ser	Cys	His	Pro	Ile	Val	Ser	Phe	Arg	His	Leu	
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	Asp	Leu	Ser	Phe	Asn	Asp	Phe	Lys	Ala	Leu	Pro	Ile	Cys	Lys	Glu	Phe	
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	Gly	Asn	Leu	Ser	Gln	Leu	Asn	Phe	Leu	Gly	Leu	Ser	Ala	Met	Lys	Leu	
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	Gln	Lys	Leu	Asp	Leu	Leu	Pro	Ile	Ala	His	Leu	His	Leu	Ser	Tyr	Ile	
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	Leu	Leu	Asp	Leu	Arg	Asn	Tyr	Tyr	Ile	Lys	Glu	Asn	Glu	Thr	Glu	Ser	
		145				150					155						
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	Leu	Gln	Ile	Leu	Asn	Ala	Lys	Thr	Leu	His	Leu	Val	Phe	His	Pro	Thr	
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40	agt	tta	ttc	gct	atc	caa	gtg	aac	ata	tca	gtt	aat	act	tta	ggg	tgc	733
	Ser	Leu	Phe	Ala	Ile	Gln	Val	Asn	Ile	Ser	Val	Asn	Thr	Leu	Gly	Cys	
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45	tta	caa	ctg	act	aat	att	aaa	ttg	aat	gat	gac	aac	tgt	caa	gtt	ttc	781
	Leu	Gln	Leu	Thr	Asn	Ile	Lys	Leu	Asn	Asp	Asp	Asn	Cys	Gln	Val	Phe	
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	Ile	Lys	Phe	Leu	Ser	Glu	Leu	Thr	Arg	Gly	Pro	Thr	Leu	Leu	Asn	Phe	
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	Thr	Leu	Asn	His	Ile	Glu	Thr	Thr	Trp	Lys	Cys	Leu	Val	Arg	Val	Phe	
		225					230				235						
60	caa	ttt	ctt	tgg	ccc	aaa	cct	gtg	gaa	tat	ctc	aat	att	tac	aat	tta	925
	Gln	Phe	Leu	Trp	Pro	Lys	Pro	Val	Glu	Tyr	Leu	Asn	Ile	Tyr	Asn	Leu	
		240				245					250					255	
65	aca	ata	att	gaa	agc	att	cgt	gaa	gaa	gat	ttt	act	tat	tct	aaa	acg	973
	Thr	Ile	Ile	Glu	Ser	Ile	Arg	Glu	Glu	Asp	Phe	Thr	Tyr	Ser	Lys	Thr	
					260				265						270		
70	aca	ttg	aaa	gca	ttg	aca	ata	gaa	cat	atc	acg	aac	caa	gtt	ttt	ctg	1021
	Thr	Leu	Lys	Ala	Leu	Thr	Ile	Glu	His	Ile	Thr	Asn	Gln	Val	Phe	Leu	
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	ttt tca cag aca gct ttg tac acc gtg ttt tct gag atg aac att atg	1069
	Phe Ser Gln Thr Ala Leu Tyr Thr Val Phe Ser Glu Met Asn Ile Met	
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	Met Leu Thr Ile Ser Asp Thr Pro Phe Ile His Met Leu Cys Pro His	
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10	gca cca agc aca ttc aag ttt ttg aac ttt acc cag aac gtt ttc aca	1165
	Ala Pro Ser Thr Phe Lys Phe Leu Asn Phe Thr Gln Asn Val Phe Thr	
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	Asp Ser Ile Phe Glu Lys Cys Ser Thr Leu Val Lys Leu Glu Thr Leu	
	340 345 350	
20	atc tta caa aag aat gga tta aaa gac ctt ttc aaa gta ggt ctc atg	1261
	Ile Leu Gln Lys Asn Gly Leu Lys Asp Leu Phe Lys Val Gly Leu Met	
	355 360 365	
25	acg aag gat atg cct tct ttg gaa ata ctg gat gtt agc tgg aat tct	1309
	Thr Lys Asp Met Pro Ser Leu Glu Ile Leu Asp Val Ser Trp Asn Ser	
	370 375 380	
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	Val Val Leu Asn Leu Ser Ser Asn Met Leu Thr Asp Ser Val Phe Arg	
	400 405 410 415	
35	tgt tta cct ccc agg atc aag gta ctt gat ctt cac agc aat aaa ata	1453
	Cys Leu Pro Pro Arg Ile Lys Val Leu Asp Leu His Ser Asn Lys Ile	
	420 425 430	
40	aag agc gtt cct aaa caa gtc gta aaa ctg gaa gct ttg caa gaa ctc	1501
	Lys Ser Val Pro Lys Gln Val Val Lys Leu Glu Ala Leu Gln Glu Leu	
	435 440 445	
45	aat gtt gct ttc aat tct tta act gac ctt cct gga tgt ggc agc ttt	1549
	Asn Val Ala Phe Asn Ser Leu Thr Asp Leu Pro Gly Cys Gly Ser Phe	
	450 455 460	
	agc agc ctt tct gta ttg atc att gat cac aat tca gtt tcc cac cca	1597
	Ser Ser Leu Ser Val Leu Ile Ile Asp His Asn Ser Val Ser His Pro	
	465 470 475	
50	tcg gct gat ttc ttc cag agc tgc cag aag atg agg tca ata aaa gca	1645
	Ser Ala Asp Phe Phe Gln Ser Cys Gln Lys Met Arg Ser Ile Lys Ala	
	480 485 490 495	
55	ggg gac aat cca ttc caa tgt acc tgt gag cta aga gaa ttt gtc aaa	1693
	Gly Asp Asn Pro Phe Gln Cys Thr Cys Glu Leu Arg Glu Phe Val Lys	
	500 505 510	
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5	tat	aag	tgt	gac	tac	cca	gaa	agt	tat	aga	gga	agc	cca	cta	aag	gac	1789
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10	ttt	cac	atg	tct	gaa	tta	tcc	tgc	aac	ata	act	ctg	ctg	atc	gtc	acc	1837
	Phe	His	Met	Ser	Glu	Leu	Ser	Cys	Asn	Ile	Thr	Leu	Leu	Ile	Val	Thr	
			545				550					555					
15	atc	ggt	gcc	acc	atg	ctg	gtg	ttg	gct	gtg	act	gtg	acc	tcc	ctc	tgc	1885
	Ile	Gly	Ala	Thr	Met	Leu	Val	Leu	Ala	Val	Thr	Val	Thr	Ser	Leu	Cys	
			560				565				570					575	
20	atc	tac	ttg	gat	ctg	ccc	tgg	tat	ctc	agg	atg	gtg	tgc	cag	tgg	acc	1933
	Ile	Tyr	Leu	Asp	Leu	Pro	Trp	Tyr	Leu	Arg	Met	Val	Cys	Gln	Trp	Thr	
					580					585					590		
25	cag	act	cgg	cgc	agg	gcc	agg	aac	ata	ccc	tta	gaa	gaa	ctc	caa	aga	1981
	Gln	Thr	Arg	Arg	Arg	Ala	Arg	Asn	Ile	Pro	Leu	Glu	Glu	Leu	Gln	Arg	
					595				600					605			
30	aac	ctc	cag	ttt	cat	gct	ttt	att	tca	tat	agt	gaa	cat	gat	tct	gcc	2029
	Asn	Leu	Gln	Phe	His	Ala	Phe	Ile	Ser	Tyr	Ser	Glu	His	Asp	Ser	Ala	
			610					615					620				
35	tgg	gtg	aaa	agt	gaa	ttg	gta	cct	tac	cta	gaa	aaa	gaa	gat	ata	cag	2077
	Trp	Val	Lys	Ser	Glu	Leu	Val	Pro	Tyr	Leu	Glu	Lys	Glu	Asp	Ile	Gln	
			625				630					635					
40	att	tgt	ctt	cat	gag	agg	aac	ttt	gtc	cct	ggc	aag	agc	att	gtg	gaa	2125
	Ile	Cys	Leu	His	Glu	Arg	Asn	Phe	Val	Pro	Gly	Lys	Ser	Ile	Val	Glu	
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50	tct	ccc	aac	ttt	gtc	cag	agt	gag	tgg	tgc	cat	tac	gaa	ctc	tat	ttt	2221
	Ser	Pro	Asn	Phe	Val	Gln	Ser	Glu	Trp	Cys	His	Tyr	Glu	Leu	Tyr	Phe	
				675					680					685			
55	gcc	cat	cac	aat	ctc	ttt	cat	gaa	cga	tct	aat	aac	tta	atc	ctc	atc	2269
	Ala	His	His	Asn	Leu	Phe	His	Glu	Gly	Ser	Asn	Asn	Leu	Ile	Leu	Ile	
				690				695					700				
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	Leu	Leu	Glu	Pro	Ile	Pro	Gln	Asn	Ser	Ile	Pro	Asn	Lys	Tyr	His	Lys	
			705				710					715					
65	ctg	aag	gct	ctc	atg	acg	cag	cgg	act	tat	ttg	cag	tgg	ccc	aag	gag	2365
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 5 10 15
 Asp Leu Pro Leu Lys Thr Lys Val Leu Asp Met Ser Gln Asn Tyr Ile
 35 20 25 30
 Ala Glu Leu Gln Val Ser Asp Met Ser Phe Leu Ser Glu Leu Thr Val
 35 40 45
 40 Leu Arg Leu Ser His Asn Arg Ile Gln Leu Leu Asp Leu Ser Val Phe
 50 55 60 65
 Lys Phe Asn Gln Asp Leu Glu Tyr Leu Asp Leu Ser His Asn Gln Leu
 70 75 80
 45 Gln Lys Ile Ser Cys His Pro Ile Val Ser Phe Arg His Leu Asp Leu
 85 90 95
 Ser Phe Asn Asp Phe Lys Ala Leu Pro Ile Cys Lys Glu Phe Gly Asn
 50 100 105 110
 Leu Ser Gln Leu Asn Phe Leu Gly Leu Ser Ala Met Lys Leu Gln Lys
 115 120 125
 55 Leu Asp Leu Leu Pro Ile Ala His Leu His Leu Ser Tyr Ile Leu Leu

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5	Phe Ala Ile Gln Val Asn Ile Ser Val Asn Thr Leu Gly Cys Leu Gln		
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10	Leu Thr Asn Ile Lys Leu Asn Asp Asp Asn Cys Gln Val Phe Ile Lys		
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	Phe Leu Ser Glu Leu Thr Arg Gly Pro Thr Leu Leu Asn Phe Thr Leu		
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15	Asn His Ile Glu Thr Thr Trp Lys Cys Leu Val Arg Val Phe Gln Phe		
	230	235	240
	Leu Trp Pro Lys Pro Val Glu Tyr Leu Asn Ile Tyr Asn Leu Thr Ile		
	245	250	255
20	Ile Glu Ser Ile Arg Glu Glu Asp Phe Thr Tyr Ser Lys Thr Thr Leu		
	260	265	270
25	Lys Ala Leu Thr Ile Glu His Ile Thr Asn Gln Val Phe Leu Phe Ser		
	275	280	285
	Gln Thr Ala Leu Tyr Thr Val Phe Ser Glu Met Asn Ile Met Met Leu		
	290	295	300
30	Thr Ile Ser Asp Thr Pro Phe Ile His Met Leu Cys Pro His Ala Pro		
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	Ser Thr Phe Lys Phe Leu Asn Phe Thr Gln Asn Val Phe Thr Asp Ser		
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35	Ile Phe Glu Lys Cys Ser Thr Leu Val Lys Leu Glu Thr Leu Ile Leu		
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40	Gln Lys Asn Gly Leu Lys Asp Leu Phe Lys Val Gly Leu Met Thr Lys		
	355	360	365
	Asp Met Pro Ser Leu Glu Ile Leu Asp Val Ser Trp Asn Ser Leu Glu		
	370	375	380
45	Ser Gly Arg His Lys Glu Asn Cys Thr Trp Val Glu Ser Ile Val Val		
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	Leu Asn Leu Ser Ser Asn Met Leu Thr Asp Ser Val Phe Arg Cys Leu		
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50	Pro Pro Arg Ile Lys Val Leu Asp Leu His Ser Asn Lys Ile Lys Ser		
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	Ala Phe Asn Ser Leu Thr Asp Leu Pro Gly Cys Gly Ser Phe Ser Ser		
	450	455	460
			465

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	Asn Pro Phe Gln Cys Thr Cys Glu Leu Arg Glu Phe Val Lys Asn Ile		500	505	510
10	Asp Gln Val Ser Ser Glu Val Leu Glu Gly Trp Pro Asp Ser Tyr Lys		515	520	525
	Cys Asp Tyr Pro Glu Ser Tyr Arg Gly Ser Pro Leu Lys Asp Phe His		530	535	540
15	Met Ser Glu Leu Ser Cys Asn Ile Thr Leu Leu Ile Val Thr Ile Gly		550	555	560
	Ala Thr Met Leu Val Leu Ala Val Thr Val Thr Ser Leu Cys Ile Tyr		565	570	575
	Leu Asp Leu Pro Trp Tyr Leu Arg Met Val Cys Gln Trp Thr Gln Thr		580	585	590
25	Arg Arg Arg Ala Arg Asn Ile Pro Leu Glu Glu Leu Gln Arg Asn Leu		595	600	605
	Gln Phe His Ala Phe Ile Ser Tyr Ser Glu His Asp Ser Ala Trp Val		610	615	620
30	Lys Ser Glu Leu Val Pro Tyr Leu Glu Lys Glu Asp Ile Gln Ile Cys		630	635	640
	Leu His Glu Arg Asn Phe Val Pro Gly Lys Ser Ile Val Glu Asn Ile		645	650	655
	Ile Asn Cys Ile Glu Lys Ser Tyr Lys Ser Ile Phe Val Leu Ser Pro		660	665	670
40	Asn Phe Val Gln Ser Glu Trp Cys His Tyr Glu Leu Tyr Phe Ala His		675	680	685
	His Asn Leu Phe His Glu Gly Ser Asn Asn Leu Ile Leu Ile Leu Leu		690	695	700
45	Glu Pro Ile Pro Gln Asn Ser Ile Pro Asn Lys Tyr His Lys Leu Lys		710	715	720
	Ala Leu Met Thr Gln Arg Thr Tyr Leu Gln Trp Pro Lys Glu Lys Ser		725	730	735
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 Arg Ile His His Leu His Asp Ser Asp Phe Ala His Leu Pro Ser Leu
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 Arg His Leu Asn Leu Lys Trp Asn Cys Pro Pro Val Gly Leu Ser Pro
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 Met His Phe Pro Cys His Met Thr Ile Glu Pro Ser Thr Phe Leu Ala
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 Val Pro Thr Leu Glu Glu Leu Asn Leu Ser Tyr Asn Asn Ile Met Thr
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	Ser	Leu	Asp	Glu	Thr	Thr	Leu	Arg	Pro	Leu	Ala	Arg	Leu	Pro	Met	Leu	
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	Tyr	Asn	Ser	Gln	Pro	Phe	Gly	Met	Gln	Gly	Val	Gly	His	Asn	Phe	Ser	
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	Phe	Val	Ala	His	Leu	Arg	Thr	Leu	Arg	His	Leu	Ser	Leu	Ala	His	Asn	
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	Asp Leu Tyr Leu His Phe Phe Gln Gly Leu Ser Gly Leu Ile Trp Leu	
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10	gac ttg tcc cag aac cgc ctg cac acc ctc ctg ccc caa acc ctg cgc	2016
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	Asn Leu Pro Lys Ser Leu Gln Val Leu Arg Leu Arg Asp Asn Tyr Leu	
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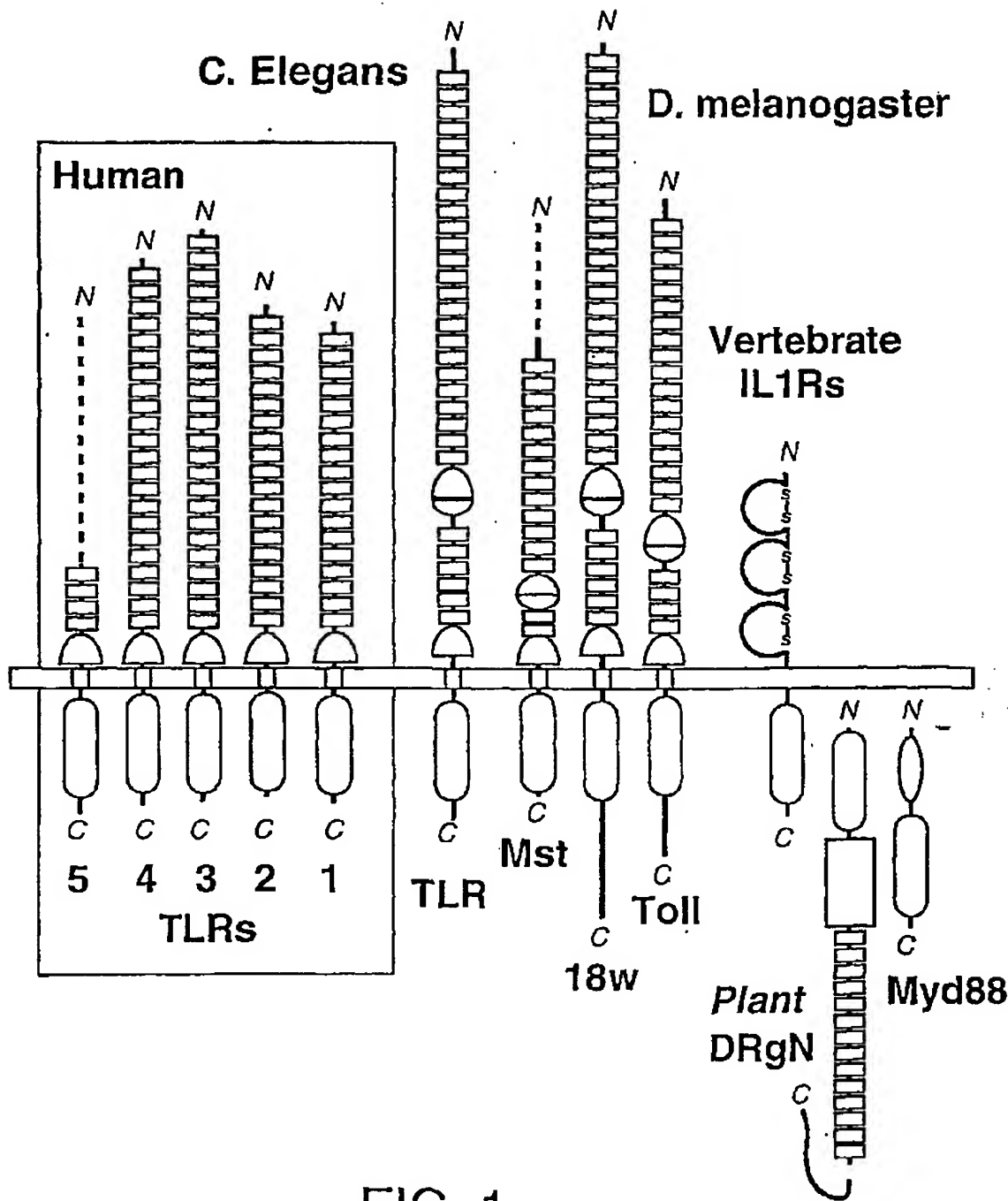
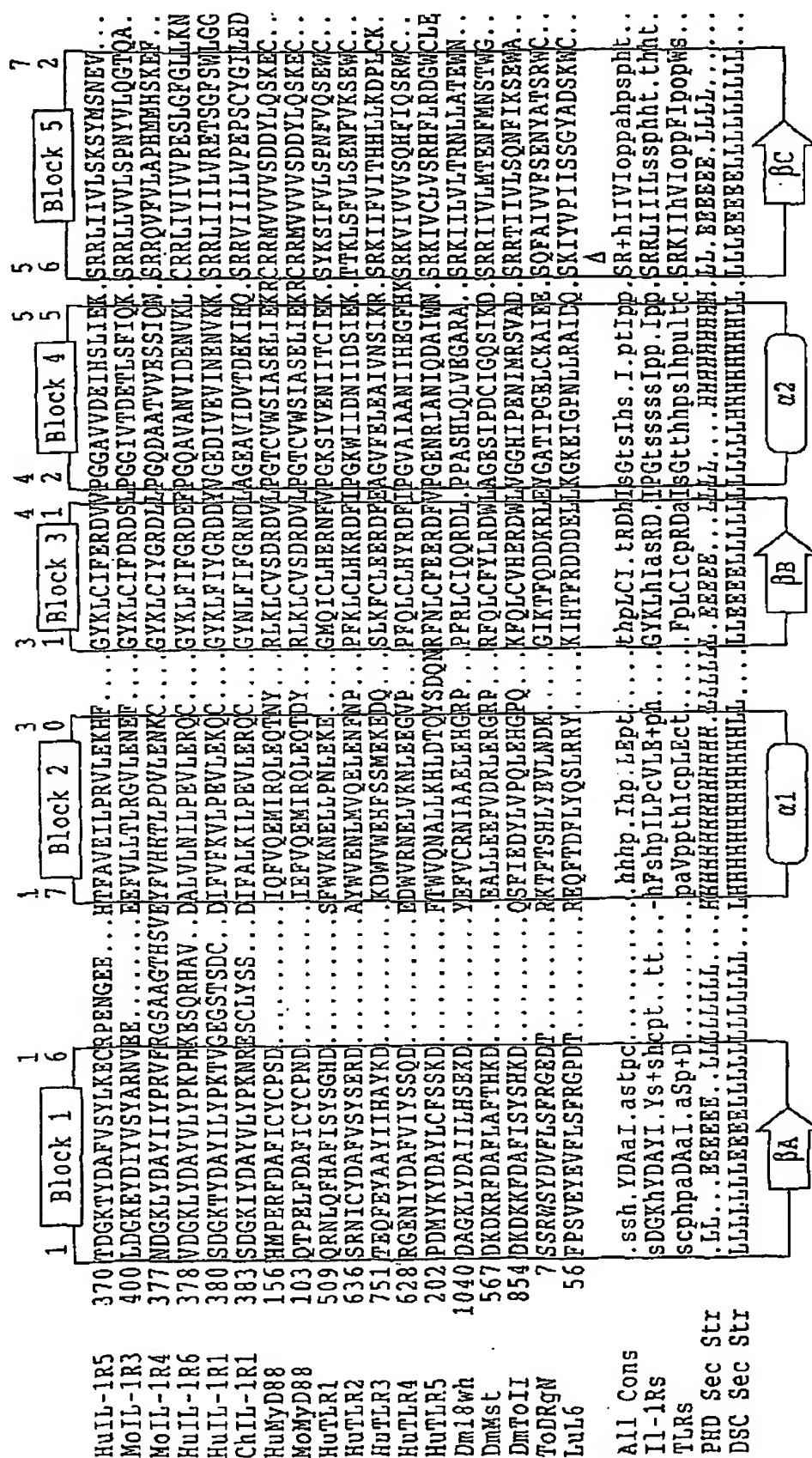


FIG. 1



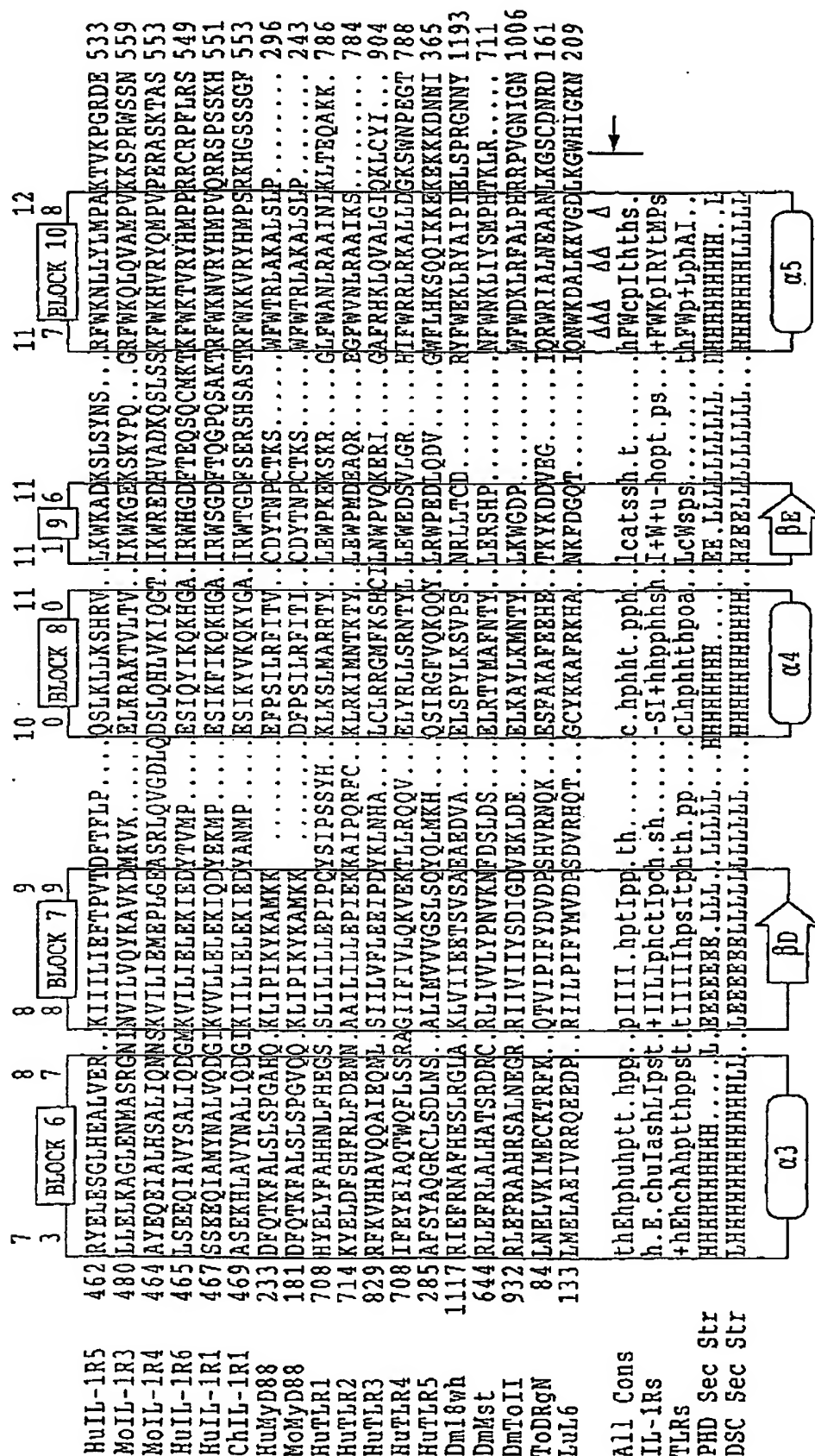


FIG. 2B

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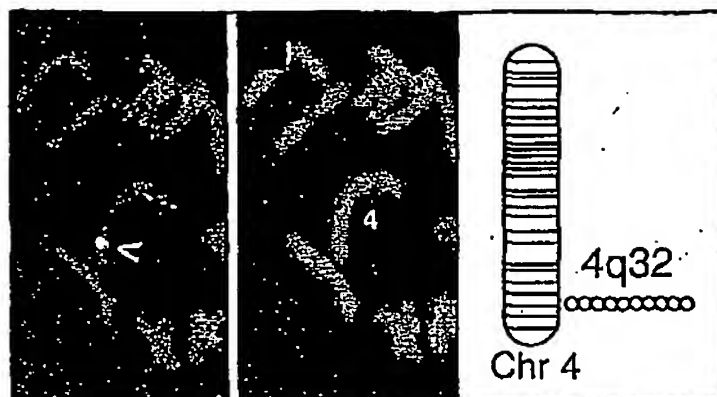


FIG. 4A

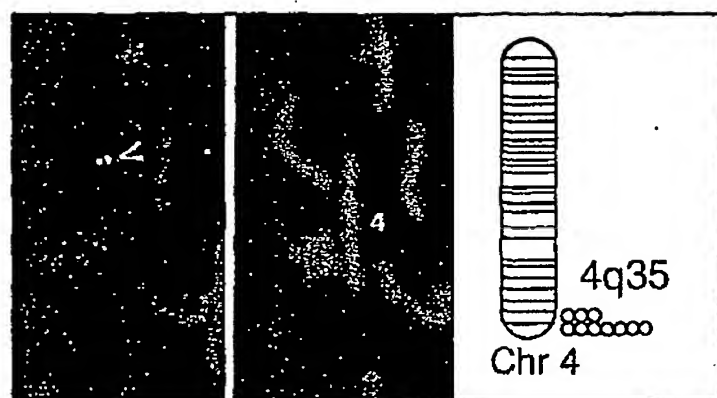


FIG. 4B

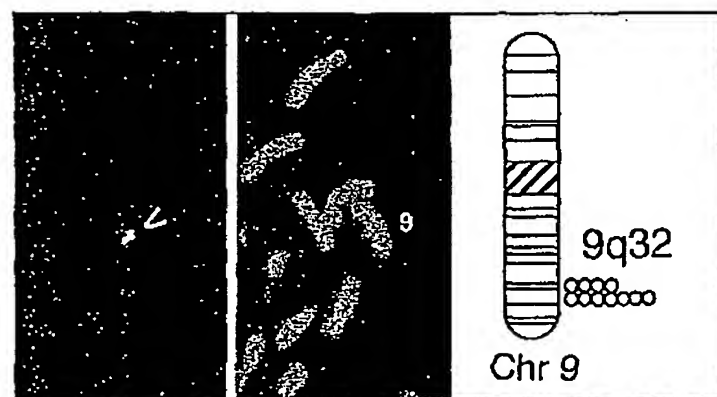


FIG. 4C

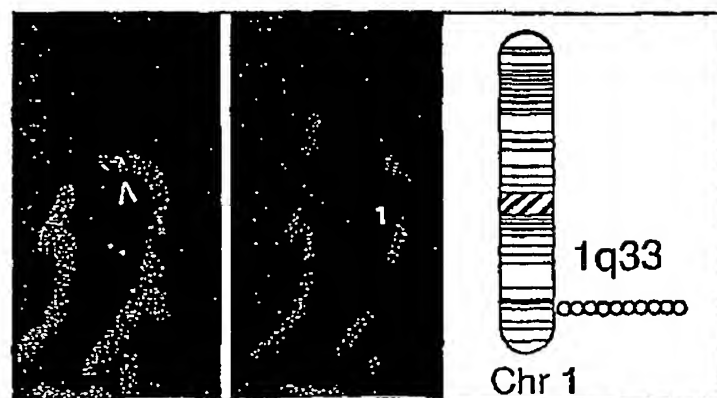
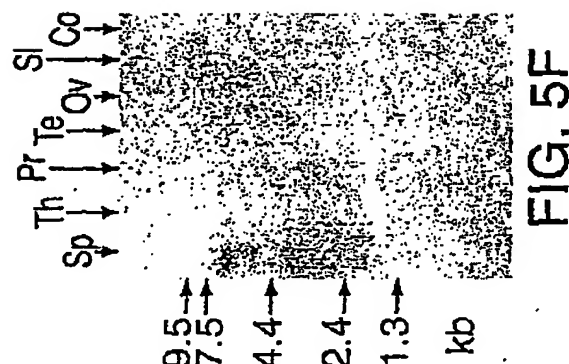
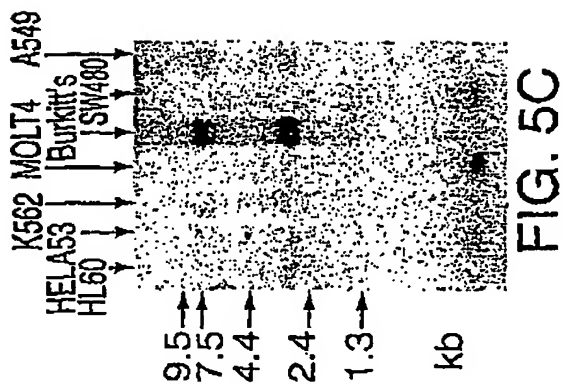
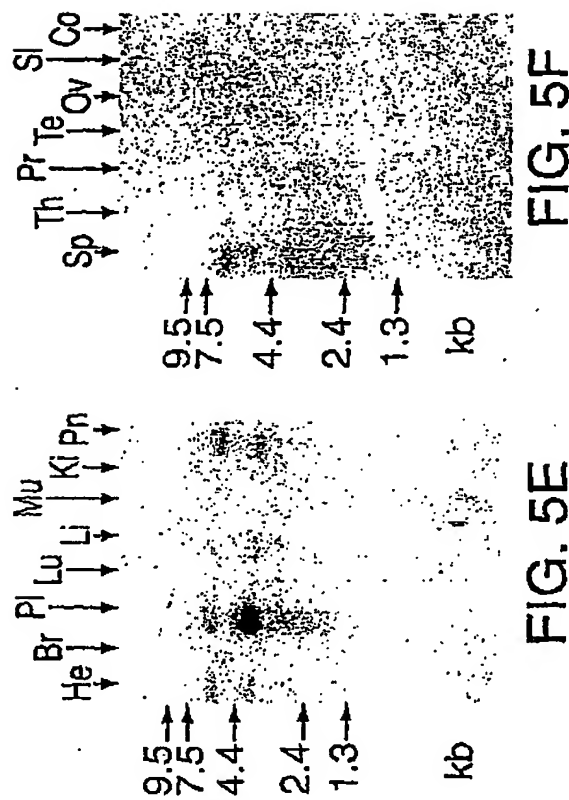
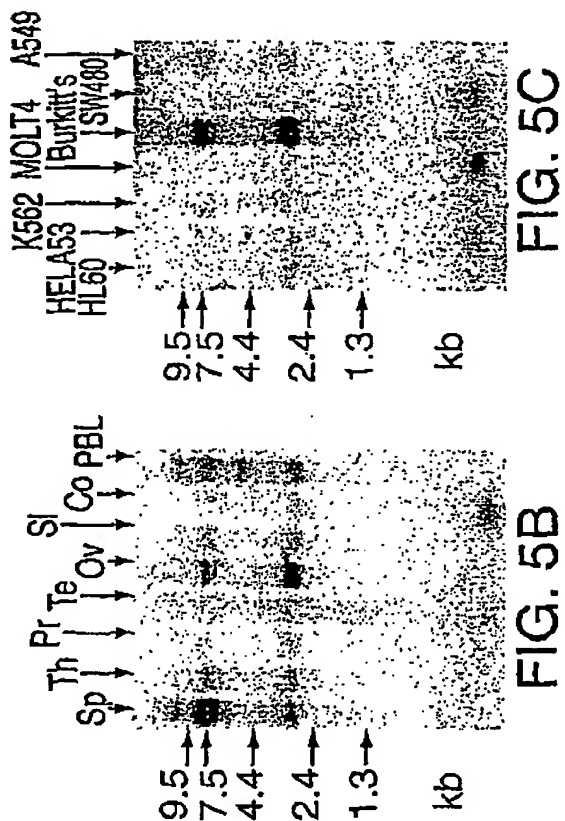
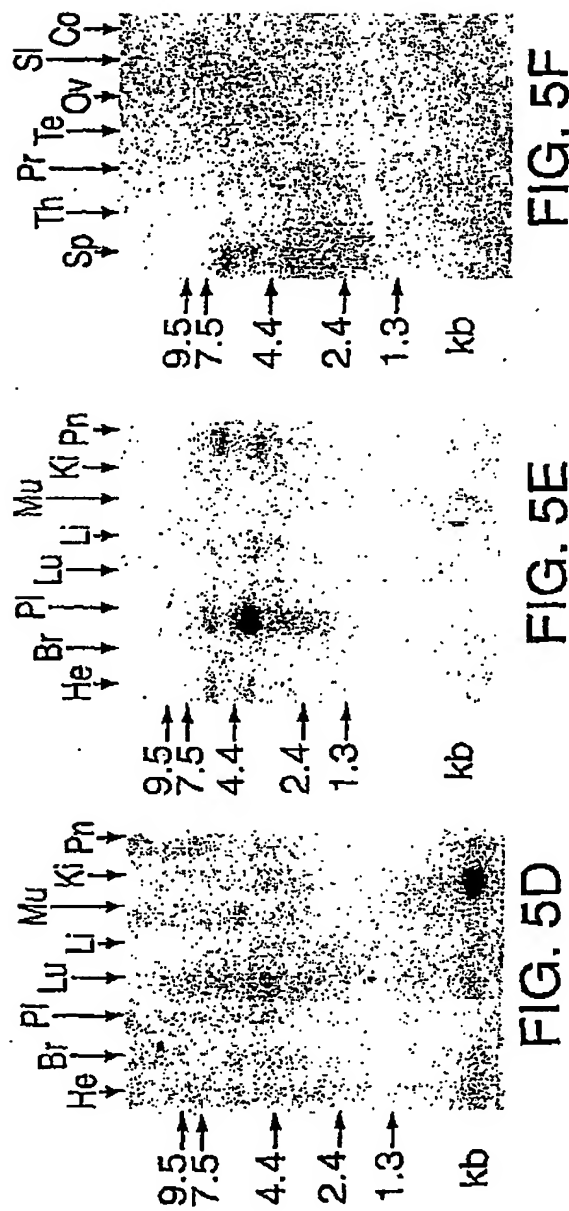
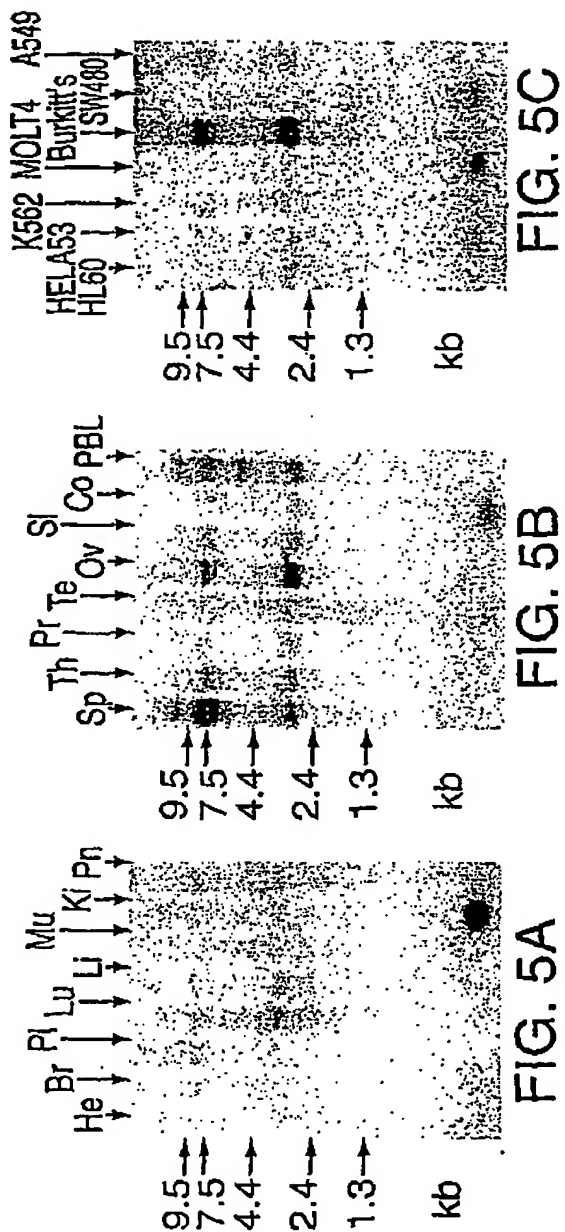


FIG. 4D



(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
29 November 2001 (29.11.2001)

PCT

(10) International Publication Number
WO 01/090151 A3

(51) International Patent Classification⁷: C07K 14/705,
16/28, C12N 15/12, 15/62, A61K 38/17, 39/395, C12N
5/10, 1/21

(21) International Application Number: PCT/US01/16766

(22) International Filing Date: 23 May 2001 (23.05.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/207,558 25 May 2000 (25.05.2000) US

(71) Applicant: SCHERING CORPORATION [US/US];
2000 Galloping Hill Road, Kenilworth, NJ 07033-0530
(US).

(72) Inventors: HARDIMAN, Gerard, T.; 11276 Woodrush
Lane, San Diego, CA 92128 (US). ROCK, Fernando, L.;
125 Cuesta Real, La Honda, CA 94020 (US). BAZAN, J.,
Fernando; 426 Waverley St., # 6, Palo Alto, CA 94301
(US). KASTELEIN, Robert, A.; 463 Summit Drive, Red-
wood City, CA 94062 (US). HO, Stephen, W. K.; 745
South Bernardo Ave., #A206, Sunnyvale, CA 94087 (US).
LIU, Yong-Jun; 4010 Villa Vista, Palo Alto, CA 94306
(US).

(74) Agent: MCLAUGHLIN, Jaye, P.; Schering-Plough Cor-
poration, Patent Dept. K-6-1 1990, 2000 Galloping Hill
Road, Kenilworth, NJ 07033 (US).

(81) Designated States (*national*): AI, AG, AI., AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CZ,
DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GR, HR, HU,
ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LU, LV,
MA, MD, MG, MK, MN, MX, MZ, NO, NZ, PL, PT, RO,
RU, SI, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UZ, VN,
YT, ZA.

(84) Designated States (*regional*): ARIPO patent (GI, GM,
KI, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, HU,
IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CI,
CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:

*as to the applicant's entitlement to claim the priority of the
earlier application (Rule 4.17(iii)) for all designations*

Published:

— with international search report

(88) Date of publication of the international search report:
17 October 2002

*For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.*

(54) Title: HUMAN RECEPTOR PROTEINS; RELATED REAGENTS AND METHODS

(57) Abstract: Nucleic acids encoding mammalian, e.g., human receptors, purified receptor proteins and fragments thereof. Anti-
bodies, both polyclonal and monoclonal, are also provided. Methods of using the compositions for both diagnostic and therapeutic
utilities are provided.

WO 01/090151 A3

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 01/16766

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07K14/705 C07K16/28 C12N15/12 C12N15/62 A61K38/17
A61K39/395 C12N5/10 C12N1/21

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12N C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, EMBL, WPI Data, PAJ, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 50547 A (SCHERING CORP) 12 November 1998 (1998-11-12) DNA Seq ID no 3, Protein Seq ID no 4. ---	1-21
X	WO 99 20756 A (GENENTECH INC ;GODDARD AUDREY (US); GODOWSKI PAUL J (US); GURNEY A) 29 April 1999 (1999-04-29) DNA Seq ID no 11, Protein Seq ID no 12. --- -/--	1-21

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Date of the actual completion of the international search

23 April 2002

Date of mailing of the international search report

26. 07. 2002

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 351 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Aslund, J

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/16766

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ROCK FERNANDO L ET AL: "A family of human receptors structurally related to <i>Drosophila</i> toll." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES, vol. 95, no. 2, 20 January 1998 (1998-01-20), pages 588-593, XP002197052 Jan. 20, 1998 ISSN: 0027-8424 Sequence of HuTLR2 in Figure 2. -& DATABASE EMBL [Online] EBI, Hinxton, UK; 3 October 1997 (1997-10-03) ROCK ET AL.: "Homo sapiens Toll-like receptor 2 (TLR2) mRNA, complete cds." Database accession no. U88878 XP002197054 the whole document	1-6, 11-18
X	CHAUDHARY PREET M ET AL: "Cloning and characterization of two toll/interleukin-1 receptor-like genes TIL3 and TIL4: Evidence for a multi-gene receptor family in humans." BLOOD, vol. 91, no. 11, 1 June 1998 (1998-06-01), pages 4020-4027, XP002197053 ISSN: 0006-4971 figure 1B	1-6, 11-18

INTERNATIONAL SEARCH REPORT

PCT/US 01/16766

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: 19, 20
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-21 (all partially)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 19, 20

Present claims 20, 21 relate to a compound (ligand, agonist, antagonist) defined by reference to a desirable characteristic or property, namely the ability of modulating physiology or development of a DTLR protein. The claim cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT only for antibodies. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to an antibody with specificity for a DTLR protein.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

Invention 1: Claims 1-21 Partially

A DTLR2 protein of Seq Id 4.
Furthermore, nucleic acids and vectors encoding and expressing said polypeptide and derivatives such as fusion proteins, transformed host cells, antibodies, pharmaceutical compositions comprising said protein or antibodies directed to it.

Invention 2: Claims 1-21 Partially

A DTLR3 protein of Seq Id 6.
Furthermore, nucleic acids and vectors encoding and expressing said polypeptide and derivatives such as fusion proteins, transformed host cells, antibodies, pharmaceutical compositions comprising said protein or antibodies directed to it.

Invention 3: Claims 1-21 Partially

A DTLR4 protein of Seq Id 8.
Furthermore, nucleic acids and vectors encoding and expressing said polypeptide and derivatives such as fusion proteins, transformed host cells, antibodies, pharmaceutical compositions comprising said protein or antibodies directed to it.

Invention 4: Claims 1-21 Partially

A DTLR5 protein of Seq Id 10.
Furthermore, nucleic acids and vectors encoding and expressing said polypeptide and derivatives such as fusion proteins, transformed host cells, antibodies, pharmaceutical compositions comprising said protein or antibodies directed to it.

Invention 5: Claims 1-21 Partially

A DTLR6 protein of Seq Id 12, 28, 30.
Furthermore, nucleic acids and vectors encoding and expressing said polypeptide and derivatives such as fusion proteins, transformed host cells, antibodies, pharmaceutical compositions comprising said protein or antibodies directed to it.

Invention 6: Claims 1-21 Partially

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

A DTLR7 protein of Seq Id 16, 18, 37.
Furthermore, nucleic acids and vectors encoding and expressing said polypeptide and derivatives such as fusion proteins, transformed host cells, antibodies, pharmaceutical compositions comprising said protein or antibodies directed to it.

Invention 7: Claims 1-21 Partially

A DTLR8 protein of Seq Id 32, 39.
Furthermore, nucleic acids and vectors encoding and expressing said polypeptide and derivatives such as fusion proteins, transformed host cells, antibodies, pharmaceutical compositions comprising said protein or antibodies directed to it.

Invention 8: Claims 1-21 Partially

A DTLR9 protein of Seq Id 22, 41.
Furthermore, nucleic acids and vectors encoding and expressing said polypeptide and derivatives such as fusion proteins, transformed host cells, antibodies, pharmaceutical compositions comprising said protein or antibodies directed to it.

Invention 9, Claims 1-21 Partially

A DTLR10 protein of Seq Id 34, 43, 45.
Furthermore, nucleic acids and vectors encoding and expressing said polypeptide and derivatives such as fusion proteins, transformed host cells, antibodies, pharmaceutical compositions comprising said protein or antibodies directed to it.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 01/16766

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